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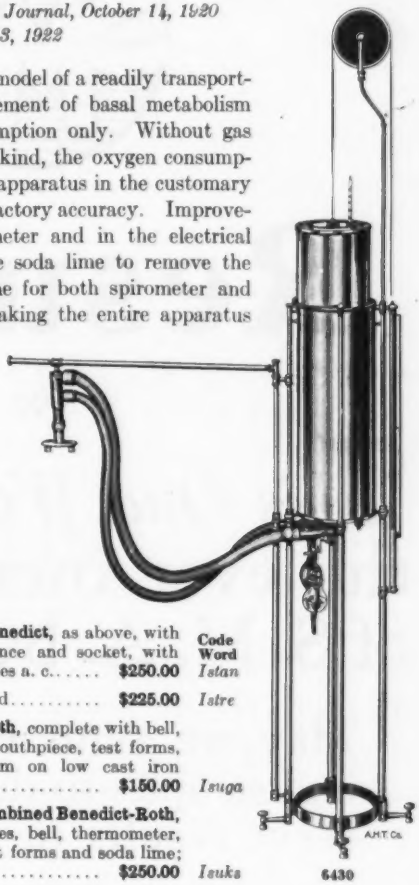

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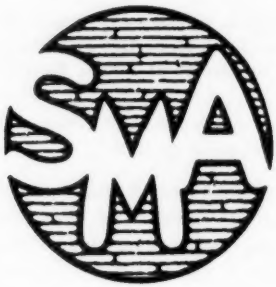

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Smallpox

a present menace

Photo, courtesy Michigan Department of Health, 1924

Smallpox is again the loathsome, disfiguring, and oft-times fatal disease it was years ago, when Jenner first advocated vaccination.

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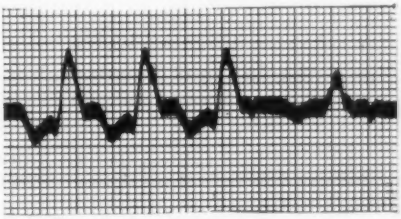

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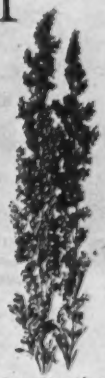

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No. IX

By. F. A. Upsher Smith, Ph. C.

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AUGUST, 1924

ORIGINAL ARTICLES.

THE USE OF TRYPARSAMIDE IN NEUROSYPHILIS.

By W. F. Lorenz, M.D., A. S. Loevenhart, M.D.,
Thos. F. Reitz, M.D.,
and
C. P. Eck, M.D.
MADISON, WIS.

Introduction. Successful results with the use of tryparsamide in neurosyphilis have been reported by Lorenz, Loevenhart, Bleckwenn and Hodges,[1] who treated cases which were mostly of institutional types. The cases herewith presented are mainly ambulatory types of neurosyphilis such as are to be found in any large dispensary, and conform with the type of case that has been studied by Moore, Robinson and Keidel.[2] Our material has been classified in accordance with the clinical types defined by the Wisconsin group. In all of our cases, the diagnosis was based upon a thorough neurological examination together with complete serological findings.

Our serological examination comprised a Wassermann test of the blood serum performed in a manner that permitted of quantitative reading. The Wassermann reaction made with the spinal fluid was also performed by making a serial dilution of the fluid ranging from 0.2 to 1 cc. In addition, a cell count was made on the fresh fluid and any excess of globulin was estimated by the Ross-Jones and Noguchi butyric acid tests. A Lange colloidal-gold test was made with each fluid. With this complete information at hand our cases were separated into the following clinical groups: paresis, atypical paresis, asymptomatic paresis, meningovascular syphilis,

tabes and taboparesis. All the cases of neurosyphilis included in our report showed a pathological spinal fluid at some time in their course.

The clinical groups are defined in the following manner:

The requirements for the diagnosis of paresis were a definite mental abnormality associated with a positive Wassermann reaction of the blood and spinal fluid, a cell count ranging from 20 to 50 per c.mm., a positive globulin test and a paretic type of "gold sol." In addition to these serological findings there had to be present some neurological abnormality in the nature of pupillary changes, disturbance of reflexes, muscular incoördinations and other signs commonly seen in paresis.

The term "atypical paresis" is reserved for the cases presenting the clinical manifestations of paresis but with a negative blood Wassermann and atypical spinal fluid findings.

The term "asymptomatic paresis" we reserved for the cases which showed the serological and neurological characteristics of paresis but in which the mental picture was lacking.

The meningovascular types were predominantly cases that presented complaints of headache and dizziness with many neurological abnormalities usually better developed in paresis but nevertheless distinctly present in this group. The spinal fluid in meningovascular syphilis is usually differentiated from the paretic type by a lesser degree of positiveness in the Wassermann test—that is, larger amounts of fluid are required for a positive response. The cell count in meningovascular syphilis ranges from normal to very high counts of 200 and more. The "gold sol" usually shows a distinctive response with the maximum reaction in the third and fourth tubes. However, one not infrequently sees the typical paretic type of curve in this group. These latter are borderline clinical cases and difficult to differentiate from asymptomatic paresis.

No definition is required for tabes or taboparesis.

After the preliminary examination referred to, all of our cases were treated with tryparsamide and mercury salicylate. The tryparsamide was administered intravenously, usually in a dosage of 3 gm.; in a few instances, 2 gm. As a rule, one injection was given each week for a period of eight weeks. The drug was dissolved in 10 cc of freshly distilled sterile water and the solution filtered through a sterile filter paper before administering. The solution was injected at room temperature within a few minutes after filtering. Mercury salicylate was given intramuscularly in doses ranging from 32 to 65 mg. ($\frac{1}{2}$ to 1 gr.). These injections were spaced midway between the tryparsamide injections and a total of 8 doses of mercury salicylate given during the period of tryparsamide injection was the usual course of treatment.

The majority of our cases had received other forms of antiluetic treatment before tryparsamide and mercury was used. In general,

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however, the results from previous treatment had been poor and our effort with this new drug was clearly warranted.

In all, we are reporting on 185 cases. The earlier cases have been in our hands since the spring of 1922. Many of our later cases, while included in this report, are still under treatment so that our results for the more recent cases cannot be regarded as final. However, considerable information has been obtained as the result of our efforts and the usefulness of this drug is further emphasized by our experience.

Paresis. We are reporting on 84 cases of paresis. While these were all ambulatory types, 9 were sufficiently psychotic, in our judgment, to warrant institutional supervision. Among the others some were distinctly euphoric and even delusional, with memory defects and other evidence of mental deterioration. In the majority of cases the mental symptoms were not so marked as to be recognized as a psychosis or detected as a grossly abnormal reaction. They might easily pass for normal. Yet, upon close inspection and inquiry ample evidence of reduced capacity for work, change in character, indifference, and lessened interests could be elicited. A small number were distinctly depressed. Others appeared dejected, and not infrequently expressed an awareness of mental confusion. Fatigability was frequently complained of by these less psychotic types. It is remarkable to note the frequency with which a distinct recognition of failing mental power is expressed by these early paretics. Probably one only sees these mental states in a dispensary practice.

It should be emphasized that in addition to the usual neurological signs of paresis, all of these cases showed a completely positive serology before treatment with tryparsamide and mercury.

The clinical results of treatment in this group are as follows: 37 cases (41 per cent) were mentally restored; 38 cases (42 per cent) were distinctly improved; 9 cases (10 per cent) remained unchanged; 6 cases (7 per cent) mental manifestations progressed.

By mental restoration we mean the disappearance of the mental symptoms noted before treatment which, in many cases, was further evidenced by a distinct increase in earning power. This change is invariably noticed by the patient himself as well as by those with whom he is closely associated, such as members of his family.

The effect of treatment on the serology was less marked. The blood Wassermann became negative in 49 cases (54 per cent); was reduced in 17 cases (19 per cent); remained stationary in 15 cases (17 per cent), and became more positive in 3 cases (3 per cent).

The spinal fluid findings were less influenced. In 6 cases (7 per cent) the fluid became completely normal. In 36 cases (40 per cent) a very marked improvement was noted. The cell content, which is most easily influenced by any form of treatment, fell to normal and greater amounts of fluid were required to bring about a positive Wassermann reaction.

The "gold sol" changed from the paretic type to that more frequently seen in meningovascular syphilis. In 24 cases (27 per cent) a final lumbar puncture could not be obtained. Of the remaining 17 cases (19 per cent) the spinal fluid serology remained practically unchanged, except for a reduction in cell count and some slight changes in the "gold sol" curve. These fluids were regarded as being uninfluenced. Most of these cases are still under treatment. In general a total of 24 gm. within a period of two months is required for any pronounced serological effect.

It is to be noted that the 6 cases with completely normal fluids after treatment with tryparsamide are among the cases that were restored clinically and that generally the cases which showed the maximum clinical improvement likewise showed the greatest serological improvement. There were two exceptions to this rule. One case showed an excellent clinical result after two courses consisting of 8 doses of 3 gm. each in which the blood and spinal fluid serology remained practically unchanged. The other case was one which showed complete clinical recovery after 3 courses of treatment, but in which the blood and spinal fluid were more positive serologically after the treatment. In both of these cases further therapeutic efforts will be made because it is feared that a strongly positive serology points to disease activity and therapy should be continued but possibly modified to meet the particular problem that presents itself.

Physical signs were but slightly influenced. However, the vast majority showed general improvement as evidenced by a gain in weight and improved general health and vigor. Some cases showed better muscular control and coördination, less disturbance of speech and less evident tremors. Pupillary anomalies remained practically unchanged.

The 36 cases that were mentally restored received from 16 to 48 doses of tryparsamide and mercury salicylate. All cases were started with 3 gm. In 2 cases the treatment was interrupted because of amblyopia but subsequently tryparsamide was resumed.

Paresis with Atypical Serology. Of the 90 paretics, we had 6 cases which from their mental and neurological findings would be clinically diagnosed as paretics, but in which the blood was negative and the spinal fluid atypical. These cases gave a history of intensive antiluetic treatment over a period of years. One of these cases presented the picture of paretic dementia that is usually found in the infirmary of a State Hospital. This particular case made a remarkable recovery after 16 injections of tryparsamide. The other 5 cases showed some improvement in their mental condition.

Asymptomatic Paresis. These cases showed the serological findings of paresis without mental derangement. Neurological symptoms were present in the nature of pupillary anomalies, disturbance of deep reflexes, tremors and frequently speech defects. These

cases can only be recognized as the result of routine spinal fluid examinations in all cases of positive blood in which syphilis has apparently been latent for long periods. The blood is very positive and the spinal fluid Wassermann is likewise positive with small amounts. The cell count is similar to that of paresis and the globulin tests are positive. In order to class the case as asymptomatic paresis, it was required that the "gold sol" be of the paretic type.

As these cases are predominantly serological conditions associated with physical signs which are slightly, if at all, affected by any antiluetic treatment, the evidence of therapeutic effect therefore must be sought in the serology.

We include 23 cases of asymptomatic paresis in this report. As the result of treatment with tryparsamide and mercury, the blood Wassermann became negative in 19 cases. Of these, the spinal fluid of one became completely negative after 16 injections of 3 gm. each of tryparsamide. In 6 cases the spinal fluid was very markedly improved. The cell count was reduced to the normal range, the globulin tests became negative or only very faintly positive, and the Wassermann reaction either became completely negative or a positive reaction was obtained only with large amounts of fluid where small amounts had previously given a similar response. There was also a disappearance of the paretic type of "gold sol" reaction but a persistence of a reaction simulating that usually found in meningovascular syphilis. As a rule, the "gold sol" is favorably influenced early in the treatment but remains positive longer than the Wassermann test. In the 12 remaining cases in which the blood became negative, unfortunately lumbar punctures could not be obtained. It is possible that among these 12 patients, other cases of marked improvement in spinal fluid serology might have been found. It must be borne in mind that these patients suffer no symptoms. They are not very much worried about their condition and it is difficult to hold them for repeated lumbar punctures and other examinations.

Four cases showed practically no change in the blood or spinal fluid after 16 injections of tryparsamide and mercury. In 1 case the progress of the disease was apparently hastened. Definite mental symptoms developed during the second period of treatment. This patient was later committed to a State institution and no subsequent examination of the spinal fluid could be made.

Meningovascular Syphilis. In this group one has a clinical as well as a serological situation to observe during treatment. Here the patient suffers discomforts and evidences of improvement in his condition are both objective and subjective.

Twenty-nine cases were diagnosed as meningovascular syphilis. Of these 19 (66 per cent) recovered. The amount of treatment in these ranged from $2\frac{1}{2}$ to 5 courses or from 20 to 40 injections of tryparsamide over a period of from eight to twenty months. Seven cases were very much benefited but 3 remained unimproved.

In this group all the cases, with one exception, showed a positive spinal fluid before treatment was started. Before treatment 6 of the 29 cases had a negative blood with a positive spinal fluid. In 5 of the clinical recoveries both the blood and spinal fluid became completely negative. This represents 17 per cent in which a perfect result was obtained. In 13 cases of clinical recovery the fluid was markedly improved; in 7 cases it was favorably affected. The blood Wassermann became negative in 11 cases or approximately 48 per cent after 16 to 24 injections of tryparsamide. One of the cases included in the recoveries complained of severe headache, dizziness and mental fatigue and showed unequal pupils and exaggerated deep reflexes. His serology was negative before treatment. During the previous three years, this patient had received 20 injections of neoarsphenamin and over 40 injections of mercury. He was placed on tryparsamide in 3 gm. doses but no mercury was used. After 8 injections the symptoms had completely disappeared.

Tabes and Taboparesis. There are 43 cases of tabes and taboparesis included in this report. Of these, 14 showed definite mental symptoms which constitute the outstanding clinical manifestations. Mental restoration occurred in 3 of these cases, 7 improved and 4 remained practically unchanged. The 3 cases that showed the maximum mental restoration also showed the greatest serological improvement.

Of the 43 cases, 29 were tabetics. Most of these patients presented themselves for treatment because of severe crises. All had had previous antiluetic treatment without benefit. Ten cases were greatly relieved and claims of better health, better muscular control and general improvement were made by these patients. In 3 cases which were entirely relieved of pain, the improvement in muscular coördination was very evident. These patients had received from 32 to 40 injections of tryparsamide in 3 gm. doses.

The serological results in these cases were as follows: Sixteen of the 29 cases showed a positive blood before treatment: ten of these became negative after 2 to 3 courses.

Twenty-seven of the 29 cases showed a pathological spinal fluid but less marked than in paresis; that is, in some instances the "gold sol" alone was positive with a Wassermann reaction only positive with larger amounts of fluid and not infrequently with a normal cell count or only faintly positive globulin tests. In 3 cases the fluid became completely negative and in 16 cases decided improvement was noted.

In 16 of the 29 tabetics (55 per cent), treatment with tryparsamide and mercury was ineffective clinically. Two cases progressed rapidly and treatment was discontinued during the second course.

Visual Disturbance. Visual disturbance due to tryparsamide has been reported by Louise Pearce[3] and by Lorenz, Loevenhart, Bleckwenn and Hodges.[1] All the cases treated by us were examined

before and during the period of treatment, The eye-grounds were frequently studied and the patient was tested for visual acuity. Inquiries as to visual embarrassment were frequently made during the course of treatment. There were no visual disturbances in the 23 cases of asymptomatic paresis. Among the 29 cases of meningovascular syphilis, 1 case developed very mild amblyopia. Treatment with tryparsamide was interrupted for two weeks and this symptom disappeared. The case was then carried on 2 gm. and later 3 gm. doses, as in the beginning, without developing any further visual disturbance. Of the 84 paretics, 2 cases developed amblyopia after 3 and 4 injections, respectively, of 3 gm. of tryparsamide. In both instances treatment was withheld for three weeks and then gradually resumed until the original 3 gm. dose was again being used. No further visual disturbance developed in these cases. Two cases of taboparesis developed amblyopia during the first course of treatment. Both of these were promptly relieved by withholding the drug for two weeks. As in the other cases mentioned treatment with tryparsamide was gradually resumed and continued without further trouble. Four cases of tabes developed a mild amblyopia and after a rest period treatment with tryparsamide was resumed without further visual disturbance.

In 4 cases a severe degree of visual disturbance occurred during the first course of treatment. Three of these were taboparetics and the other a case of tabes. In 1 case of taboparesis very definite optic atrophy was noted before treatment. In this case after 3 injections of 1 gm. the patient was able to distinguish only between light and darkness. The case has disappeared and we are unable to report the final condition. The other 3 cases of severe amblyopia were given no tryparsamide for one month. The visual acuity returned and these cases were then started on 1 gm. doses of tryparsamide. After 3 injections the dose was increased to 2 gm. and these patients were then continued on this dosage without any further recurrence of visual disturbance.

In all, 13 of the 185 cases of neurosyphilis or approximately 7 per cent showed visual disturbances. Nine of these cases were very mild and 4 were severe reactions. In 12 of 13 cases, all visual disturbances disappeared when the drug was stopped and all of these cases were subsequently treated with the original dose after they had been rested from two to four weeks.

It is noteworthy that the 4 severe cases developed in tabes and taboparesis and, further, that 6 of the milder reactions occurred in this group. A total of 10 of the 13 cases of visual disturbance occurred in tabetics and taboparetics and clearly points to the type of clinical case that must be watched with the greatest care.

The relationship of tryparsamide and other therapeutically used arsenicals to amblyopia is a problem that is being investigated by various members of our group. Extensive animal experimentation

by Young and Loevenhart[4] has led to certain conclusions which will soon be reported. Another effort has been a special study in a large group of clinical cases by Bleckwenn and Neff. At this time we reiterate the need of careful eye examination before and during tryparsamide administration and the prompt withdrawal of this drug when amblyopia develops.

SUMMARY OF RESULTS OF THE THERAPEUTIC USE OF TRYPARSAMIDE IN NEUROSYPHILIS.

Classification.	Clinically.				Blood Wassermann.				Spinal fluid serology.			
	Restored.	Improved.	Unimproved.	Aggravated.	Negative.	Improved.	Unchanged.	More positive.	Negative.	Improved.	Unchanged.	Aggravated.
Paresis (90 cases)	37	38	9	6	49[1]	17	15	3	6[2]	36	17	
Paresis, asymptomatic (23 cases) . . .	There are no psychotic manifestations in this group. One case developed a psychosis during treatment.				19	..	4	..	1	6	4[3]	
Meningovascular syphilis (29 cases) . . .	19	7	3	..	11[4]	6	6	..	5[5]	20		
Taboparesis (14 cases) . . .	3	7	4	..	5[6]	2	2	..	1	10	3	
	(Psychotic cases only included.)											
Tabes (29 cases)	3	10	14	2	10[7]	..	6	..	3	16	10	

[1] Six cases had a negative blood before treatment with tryparsamide and are not included in the table.

[2] The table does not include the spinal-fluid findings in the 6 atypical cases and the 24 cases in which a final lumbar puncture was not obtained.

[3] There were 12 cases in which final puncture was not obtained.

[4] In 6 cases the blood was negative before treatment.

[5] In 4 cases a final puncture was not obtained.

[6] In 5 cases the blood was negative before treatment.

[7] Thirteen cases were negative before treatment began.

Conclusions. As a result of our efforts in 185 cases of neurosyphilis treated over a two-year period, we conclude:

1. Tryparsamide and mercury salicylate are therapeutically effective in early paresis, meningovascular syphilis, and, to a lesser extent, in taboparesis, tabes and in advanced paresis.

2. The beneficial clinical results generally precede the improvement in the serology.

3. Definite paretic psychoses disappear as the result of treatment.

4. The mental restoration has persisted over a two-year period.

5. Visual disturbances occurred in 7 per cent of the total number treated.

6. In tabes and taboparesis 23 per cent of the cases showed visual disturbance.

7. Of 13 cases showing amblyopia during tryparsamide therapy all but one cleared up after the withdrawal of the drug. Twelve of these cases were subsequently treated with tryparsamide without further eye disturbance.

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CORONARY SCLEROSIS: AN ANALYSIS OF EIGHTY-SIX NECROPSIES.

By Fredrick A. Willius, M.D.,

and

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In the correlation of clinical data and necropsy findings one is sometimes impressed with the paucity of subjective and objective findings in the heart indicative of serious cardiac disease, when the pathologic findings demonstrate advanced sclerosis of the coronary arteries. This study was undertaken for the purpose of determining the frequency of occult coronary disease, and to obtain data to coördinate clinical and necropsy findings. Eighty-six unselected, consecutive, proved cases of coronary sclerosis were studied.

Age. The youngest patient in the group was thirty-three years of age, and the oldest eighty-one; the average age was sixty and three-tenths years. The highest incidence occurred in the seventh decade of life, in which there were 38 patients. There were 22 patients in the sixth decade, 17 in the eighth, 4 each in the fourth and fifth, and 1 in the ninth. It was interesting to find 4 cases of coronary sclerosis in the fourth decade and a well advanced process in a young person, aged thirty-three years; there was no evidence of syphilis in this patient. Hirschfelder mentions a colored boy, aged nineteen years, with sclerotic coronary arteries. The dominance of coronary sclerosis in the later decades of life, as revealed in this study, agrees with the general impression regarding age incidence.

Sex. There were 67 males (78 per cent), and 19 females (22 per cent) in the group. The marked dominance of the disease in males supports the findings of other observers.

Symptoms. Twenty-one patients (24 per cent) had had typical attacks of angina pectoris without evidence of heart failure. They uniformly had had very marked sclerosis of the coronary arteries, and 14 (66 per cent) had had pronounced occlusion of the lumen of the vessels. Three had had myocardial infarction. Four (19 per cent) had had associated syphilis of the aorta; 1 of these had had a saccular aneurysm, 7.5 cm. in diameter, above the left coronary orifice, and the other a diffuse aneurysmal dilatation of the arch. Syphilis has been considered a common etiologic factor in coronary sclerosis, yet in reality it plays a minor part.

Two patients (2 per cent) had had atypical anginal attacks; that is, the origin and distribution of pain were in unusual regions. Both patients had had pain in the epigastrium, with a tendency to radiate upward into the lower chest. The attacks bore a distinct relationship to exertion and to eating. One patient, a man, aged forty-five years, had had marked coronary sclerosis with the orifices nearly completely occluded by advanced syphilis of the aorta. The other patient, a man, aged seventy-two years, had had a moderate degree of coronary sclerosis with slight atheroma and distinct calcareous changes of the root of the aorta and the aortic valves. It is again difficult to diagnose these atypical anginal attacks.[12] The pain may occur in the abdomen, and may simulate almost any painful surgical disease of the abdomen.[14]

Twenty-two patients (26 per cent) had displayed the clinical syndrome of progressive myocardial failure unassociated with painful attacks. Two patients in this group had had severe paroxysms of dyspnea conforming to the so-called angina pectoris sine dolore type. One patient, besides progressive exertion dyspnea, had had severe attacks of paroxysmal ventricular tachycardia. The average sclerosis of the coronary arteries in this group was not so marked as in patients having typical anginal attacks. Only 5 patients (23 per cent) had had considerable occlusion of the arteries. Three patients had had infarctions of the myocardium. Only 1 patient had had syphilis of the aorta.

The progressive myocardial-failure type of coronary sclerosis apparently results from gradual interference in the circulation of the heart, producing progressive degenerative changes in the myocardium. It is probable that the heart may receive sufficient circulation to permit it to remain functional even in the presence of considerable sclerosis of the coronary arteries if there has not been a tendency toward occlusion. The degree and extent of myocardial degeneration depends, in part at least, on the degree of arterial obliteration, and on the length of time impairment in circulation has existed.

There were 7 patients (8 per cent) who, besides the progressive myocardial failure syndrome, had had typical attacks of angina pectoris. This group is emphasized because so many patients

suffering from angina pectoris present very little objective evidence of cardiac disease, and complain only of the anginal attacks. The average degree of coronary sclerosis in this group was marked. Four patients (57 per cent) had had considerable occlusion; 1 had had infarctions in the myocardium, and 1, besides sclerosis of the coronary arteries, had had well advanced syphilitic aortitis with involvement of the aortic valves.

Thirty-four patients (40 per cent) did not present sufficient subjective or objective evidence of cardiac disease to permit the diagnosis of coronary disease; their condition is referred to as the occult coronary type of disease. Osler emphasizes this observation in his statement that a large proportion of all patients with angina pectoris have clear-cut heart sounds and a good pulse and no obvious signs of cardiac disease, yet the coronary arteries may be extensively diseased. In this group the average degree of coronary sclerosis was considerably less than in the foregoing groups. Only 5 patients (15 per cent) had revealed evidence of coronary occlusion. There was none with myocardial infarction. One patient had had syphilitic arteriosclerosis of the aorta.

This important group of 34 patients deserves detailed consideration, as 40 per cent of the cases, or the largest subgroup of this study, disclosed no diagnostic evidence of coronary sclerosis. Sixteen of these patients were in the seventh decade of life, 9 in the eighth, 8 in the sixth, and 1 in the fourth. The outstanding complaints and findings had been: chronic nephritis in 6 cases, carcinoma of the stomach in 4 cases, carcinoma of the large bowel in 3 cases, peritonitis in 3 cases, diabetes mellitus in 3 cases, recent cerebral hemorrhage in 2 cases, benign prostatic hypertrophy in 2 cases, and pyonephrosis, inguinal hernia, non-syphilitic aneurysm of the abdominal aorta, chronic inanition, gastric ulcer, carcinoma of the prostate, spinal-cord tumor, splenomegaly of chronic splenitis, carcinoma of the pancreas, cirrhosis of the liver, and chronic pulmonary emphysema, in 1 case each. It is evident that a considerable degree of coronary sclerosis may exist with but few clinical signs, and it is important, therefore, always carefully to consider the possibility of occult coronary disease in patients in middle and later life.

Correlation of Associated Pathologic Findings. *Aorta.* In only one instance in this series was the thoracic aorta found to be normal. There had been syphilitic aortitis in 8 cases, in 2 of which aneurysmal dilatation had occurred, saccular in 1 case and diffuse in the other. The remaining 77 cases revealed varying degrees of sclerosis, atheroma, and ulceration of the aorta. The abdominal aorta revealed similar pathologic changes, well marked in 18 cases (21 per cent). In 1 case a large non-syphilitic aneurysm had ruptured into the right retroperitoneal space.

Heart Valves. The heart valves (leaflets or rings) were diseased in 44 cases (51 per cent). There was actual arteriosclerosis or fibrous thickening of the aortic valves alone in 17 cases (20 per cent), in 2 of which syphilitic aortitis was also associated. The mitral valves alone were sclerotic or fibrous in 6 cases (7 per cent). Both the aortic and mitral valves were the seat of sclerosis or fibrosis in 17 cases (20 per cent). In 2 cases (2 per cent) the aortic, mitral, and tricuspid valves were all involved. An acute vegetative tricuspid endocarditis was present in 1 case. In 1 there was marked sclerosis of all the valves.

The appreciation of the relative frequency of sclerosis and fibrosis of the cardiac valves associated with coronary sclerosis should aid the clinician in the interpretation of the auscultatory findings in older individuals. Only too often the murmurs noted with cardiovascular arteriosclerosis, and its attendant valvular insufficiencies are interpreted as indicating chronic valvular endocarditis.

Pulmonary Artery. The pulmonary artery was found to be diseased in only 4 cases (5 per cent). In 1 case the vessel was affected by marked arteriosclerosis; in another case it was dilated and contained chicken-fat clots, and in 2 it was the seat of quite extensive thrombosis.

Myocardium. In all the cases the myocardium had undergone various degenerative changes, consisting largely of fibrosis, fatty degeneration, cloudy swelling of the muscle bundles, segmentation, and fragmentation, and in 2 cases necrosis, in 1 of which brown atrophy had occurred. Seven cases (8 per cent) showed infarction of the myocardium. The weights of 63 hearts were recorded. The lowest weight was 140 gm. the highest, 1925 gm., and the average 472 gm.

Pericardium. The pericardium was diseased in 8 cases (9 per cent). Chronic adhesive pericarditis had occurred in 4, chronic fibrinous pericarditis in 2, and terminal fibrinous pericarditis and obliterating tuberculous pericarditis in 1.

Peripheral Arteriosclerosis. Sclerosis of the peripheral arteries was noted in 60 cases (70 per cent).

Renal Arteriosclerosis. Renal arteriosclerosis had occurred in 32 cases (37 per cent).

Cerebral Arteriosclerosis. The brains of 15 patients were examined and 13 of them revealed arteriosclerotic vessels.

Nephritis. Forty-six patients (53 per cent) had had varying degrees of chronic nephritis.

Disease of the Gall-bladder. Chronic cholecystitis, with or without stones, had occurred in 22 cases (26 per cent). This high incidence is probably partly coincidental, and partly due to the fact that the disease so often manifests itself in middle or later life, when arterial degenerative changes become evident. The association of disease of the gall-bladder with sclerosis of the coronary arteries sometimes

renders a correct diagnosis difficult, especially if the anginal attacks are atypical as regards distribution of pain.

Association of Hypertension and Coronary Sclerosis. The association of hypertension and coronary sclerosis is generally considered very unfavorable, especially in cases of angina pectoris. The added load cast on the heart by well advanced hypertension is considerable, and obviously enhances fatigue and degenerative changes of the myocardium. The myocardium, in most cases of coronary sclerosis, is already the seat of disturbances in nutrition, and any added insult undoubtedly increases the rate of progression and degree of structural damage. There were 29 cases of hypertension (33 per cent) in this series. The greatest incidence had occurred in both the fifth and sixth decades of life, 12 in each, 4 in the eighth, 5 in the seventh, and 1 in the fourth. The average blood-pressure readings in the hypertension group were systolic 183, diastolic 111, and pulse pressure 72.

It is difficult to estimate accurately the incidence of hypertension in this group, because the normal blood-pressure has not yet been definitely established for persons in the later decades of life. Wildt in his studies on blood-pressure and old age has shown that, between the ages of sixty and ninety, the systolic pressure range is from 137 to 162. At over ninety years, the systolic pressure decreases, and the diastolic is relatively low and does not follow the range of the systolic. In this series, the average blood-pressure in 16 cases in the seventh decade of life was systolic 146, and diastolic 86. There was moderate hypertension in 5 cases. In the sixth decade the average systolic pressure was 154 and the diastolic 91. Definite hypertension was present in 12 cases. In the fifth decade there were 21 cases in which the average systolic pressure was 133 and the diastolic 100. There was definite hypertension in 12 cases. There were too few cases in the fourth decade to obtain average values. The average systolic pressure readings decrease with advancing age. This may be explained by the fact that death occurs at an earlier age when hypertension and coronary sclerosis are associated, or that coronary sclerosis is comparatively rarer in primary vascular hypertension than in the senile or decrescent types of arteriosclerosis. In 9 cases (33 per cent) of typical angina pectoris, there was hypertension. In the progressive myocardial failure type, 12 cases (44 per cent) of hypertension were noted, and in the occult coronary sclerosis only 6 cases (22 per cent).

Association of Hypotension and Coronary Sclerosis. There were 3 instances of associated hypotension in the seventh decade of life, 9 in the sixth, and 2 in the fifth. The low blood-pressure in several cases was apparently related to the severe myocardial insufficiency which existed at the time of the patient's examination.

Association of Obesity and Coronary Sclerosis. The frequency of the association of obesity and degenerative cardiovascular disease

prompted the inquiry into this relationship, particularly with reference to sclerosis of the coronary arteries. The height and weight of 49 patients were available, 14 (29 per cent) of whom were distinctly obese. Twelve patients were males and 2 were females.

Mode of Death in Cases of Coronary Sclerosis. The frequency with which sudden death occurs in cases of coronary sclerosis has been noted for many years. In this series death occurred suddenly in 32 cases (37 per cent). The highest incidence, 12 (38 per cent), occurred in cases of typical angina pectoris. In the other clinical types of coronary sclerosis the order of frequency of sudden death was: in occult coronary disease, 7 cases (21 per cent), in angina pectoris with progressive myocardial failure, 6 cases (19 per cent), in progressive myocardial failure, 5 cases (16 per cent), and in atypical angina pectoris, 2 cases (6 per cent.)

Sudden death in cases of angina pectoris is not unexpected, but the rather high incidence in both the progressive myocardial failure, and the occult types of coronary sclerosis, implies the necessity for more accurate diagnosis and the identification of pathologic processes underlying myocardial degenerations. One case of sudden death was not attributable to coronary disease, but resulted from the rupture of an abdominal aneurysm.

A distinct degree of coronary occlusion had occurred in 18, 56 per cent of the patients who had died suddenly, or 62 per cent of the total number, 29, who had had coronary occlusion. Five patients had had infarction of the myocardium; 71 per cent of the sudden deaths occurred in this group.

Gradual Cardiac Failure. There were 13 cases (15 per cent) in which death had resulted from gradual myocardial failure. The incidence, according to clinical types, was angina pectoris in 5 cases (38 per cent), progressive myocardial failure in 5 cases (38 per cent), occult coronary disease in 2 cases (15 per cent), and angina pectoris with progressive myocardial failure in 1 case (8 per cent). The average degree of coronary sclerosis was marked, and 5 instances of occlusion were observed. In 1 case there was myocardial infarction, and in 1 syphilis of the aorta. Twenty-four per cent of the patients with angina pectoris died from gradual progressive myocardial failure.

Death Following Operation. Death occurred following operation in 21 cases (24 per cent), but in only 1 instance was death attributable to cardiac disease. The greatest number of patients operated on, 16 (76 per cent), had had the occult type of coronary disease. The operative procedures were numerous and the causes of death varied. Four of the patients (19 per cent) had had the progressive myocardial failure type of coronary sclerosis. One patient (5 per cent) with angina pectoris had been operated on. The average degree of coronary sclerosis in these cases was moderate; in 4 cases it was considerable. There was no instance of myocardial infarction.

Death from Other Causes. Twenty patients (23 per cent) died from causes other than those enumerated. Death in 12 cases of the occult coronary type of sclerosis resulted from chronic nephritis in 3 cases, cerebral hemorrhage in 2 cases, diabetic coma in 2 cases, carcinoma of the stomach, chronic inanition, carcinoma of the pancreas, cirrhosis of the liver, and chronic pulmonary emphysema in 1 case each. Six deaths from other causes occurred in the progressive myocardial failure type. Three deaths were attributable to cerebral hemorrhage, 1 to carcinoma of the prostate, 1 to diabetic coma, and 1 to suicide. In 1 case of those patients with angina pectoris and progressive myocardial failure type the cause of death was not clear. In 1 case of angina pectoris the patient committed suicide.

Electrocardiography in Coronary Sclerosis. The electrocardiogram is frequently of great value in aiding in the identification of coronary disease. The most common graphic abnormality is the negativity of the T-wave in certain isolated or combined derivatives. These, in order of importance, are: (1) in combined Derivations I and II, (2) in Derivation I alone, (3) in combined Derivations I, II, and III, and (4) in combined Derivations II and III. Definite electrocardiographic abnormalities, largely involving the T-wave, have been observed following sudden occlusion of the coronary arteries by embolism or thrombosis.[5, 7] Smith, in his experimental coronary ligations in dogs, found quite constant alterations in the T-wave. In a previous study significant T-wave negativity was observed in 52 per cent of patients with angina pectoris.[11]

Because of the importance of obtaining data regarding the correlation of electrocardiographic and necropsy findings, we are recording this relationship in detail. Twenty-five patients (29 per cent) had had electrocardiographic examinations.

Report of Cases. Case I (A341607).—A woman, aged thirty-five years, with angina pectoris of the progressive myocardial failure type, died suddenly. The electrocardiogram revealed auricular fibrillation, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy a moderate degree of coronary sclerosis, well advanced syphilitic aortitis, and incompetency of the aortic valves were noted. There was a moderate degree of dilatation of the left ventricle.

Case II (A264780).—A man, aged forty-two years, with angina pectoris died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and no abnormalities were noted. At necropsy the coronary arteries had numerous yellow tabular plaques of intimal thickening, and the vessels were patent and slightly dilated. Well advanced syphilitic aortitis, and diffuse aneurysmal dilatation of the arch existed. The cusps of the aortic and mitral valves were markedly sclerotic. There were many fatty deposits in the muscle bundles of the myocardium, and moderately increased connective tissue between the muscle bundles. The heart weighed 590 gm.

Case III (A399560).—A woman, aged fifty-five years, with the occult coronary type of disease, died from acute endocarditis following nephrectomy for pyonephrosis. The electrocardiogram revealed sinus rhythm, and no abnormalities. At necropsy the coronary arteries were moderately sclerosed, but not occluded. There were quite marked sclerosis of the aorta and acute vegetative endocarditis of the tricuspid valve. The myocardium was soft; there was slight separation of the muscle bundles with increased connective tissue. The heart weighed 375 gm.

Case IV (A394308).—A woman, aged fifty-two years, with the progressive myocardial failure type of disease, died from uremia, following thyroidectomy for adenomatous goiter with hyperthyroidism. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy there were many raised yellow plaques of intimal thickening of the coronary arteries. There were similar changes of the intima of the aorta, extensive marked calcareous changes of the vessel, and vegetation of the right anterior cusp of the aortic valve. The myocardium was hypertrophied, of firm consistency, and brownish-red. An acute terminal fibrinous pericarditis was also noted. The heart weighed 500 gm.

Case V (A341702).—A man, aged fifty-seven years, with angina pectoris, committed suicide. The electrocardiogram revealed sinus bradycardia, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were found to be the seat of very marked and extensive sclerosis. There were syphilis of the aorta, areas of fibrosis of the muscle fibers of the ventricles, marked increase of subepicardial fat, and chronic fibrinous pericarditis.

Case VI (A344902).—A man, aged fifty-six years, with angina pectoris, died suddenly. The electrocardiogram revealed premature contractions of auricular origin and T-wave negativity in Derivation I. At necropsy the coronary arteries were very markedly sclerosed, with almost complete obliteration of the left orifice. The aorta was distinctly sclerotic, and there were numerous atheromatous ulcers and a moderate degree of myocardial degeneration. The heart weighed 400 gm.

Case VII (A386614).—A man, aged fifty-seven years, with the occult coronary type of disease, died following a herniotomy. The electrocardiogram revealed sinus rhythm and notching of the P-wave in all derivations. At necropsy marked sclerosis of the coronary arteries without occlusion was noted. The aorta likewise was very sclerotic, and there were many marked areas of ulcerating atheroma. The myocardium revealed a moderate degree of fragmentation and segmentation of the muscle bundles, and hypertrophy was marked. The left ventricle was dilated.

Case VIII (A394125).—A man, aged fifty-eight years, with angina

pectoris, died suddenly. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were found to be markedly sclerotic, and the left coronary artery was almost completely obliterated. The aorta also was very sclerotic; elevated plaques occurred throughout its entire length, certain of which, near the bifurcation of the aorta, had undergone ulceration. There was arteriosclerotic thickening of the mitral and aortic valves. The muscle fibers of the myocardium were slightly enlarged, and the bundles revealed an abnormal separation. There was distinct atrophy of the wall of the left ventricle, with marked dilatation of the cavity. The heart weighed 525 gm.

Case IX (A42825).—A man, aged fifty-three years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The initial electrocardiographic tracing revealed auricular flutter with varying degrees of block, from 2 : 1 to 4 : 1. The ventricular rate varied from 83 to 169, and the auricular rate was 338 a minute. Five days later nodal tachycardia was present, and the following day sinus rhythm with marked prolongation of the P–R interval (0.32 second), evidently due to digitalis. At necropsy a moderate degree of sclerosis of the coronary arteries, and occlusion of the left descending branch by an old thrombus were noted. The aorta was moderately sclerotic, and numerous small ulcerations were found near the bifurcation. The myocardium was soft and flabby, and there were areas of focal hyalinization and fibrosis. There were a marked degree of fibrous tissue replacement in the interventricular septum, an aneurysm of the left ventricle at the site of infarction, and chronic adhesive pericarditis. The heart weighed 925 gm.

Case X (A148902).—A man, aged fifty-two years, with angina pectoris, died suddenly. The electrocardiogram revealed sinus rhythm and T-wave negativity in all derivations. At necropsy the coronary arteries were found to be markedly sclerotic and extensively occluded by thrombosis. The aorta was nodular, and the intima, fibrous, fatty, and calcareous. The myocardium revealed extensive fatty deposits, and a considerable degree of fibrosis. There was a marked degree of hypertrophy and moderate dilatation of the left ventricle. Infarction of the interventricular septum had occurred. The left ventricle was the seat of a mural thrombus. The aortic valves were fatty, fibrous and calcareous.

Case XI (A388891).—A man, aged sixty years, with the progressive myocardial failure type of disease, died from cardiac failure and bronchopneumonia. The electrocardiogram revealed premature contractions of ventricular origin, and T-wave negativity in combined Derivations I and II. At necropsy the coronary arteries and the aorta were found to be markedly sclerotic. There was extensive arteriosclerosis of the aortic endocardium. The myocardium

revealed a slight degree of fragmentation and segmentation of the muscle fibers. The left ventricle was hypertrophied. The heart weighed 700 gm.

Case XII (A399583).—A man, aged sixty-five years, with angina pectoris, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and preponderance of the left ventricle. At necropsy sclerosis of the coronary arteries, producing almost complete obliteration, was noted. The aorta was also markedly sclerosed at its root, with atheromatous ulcers and thrombosis. A very marked sclerosis of the aortic valves occurred, producing incompetency. The myocardium showed fatty changes and a moderate degree of hypertrophy and dilatation. The endocardium of the left ventricle was diffusely thickened, showing small areas of erosion and ulceration, and a large ulcerated area to which a thrombus was attached. The heart weighed 500 gm.

Case XIII (A374229).—A man, aged sixty-three years, with the progressive myocardial failure type of disease, died in coma from diabetes mellitus. The electrocardiogram revealed sinus rhythm, diphasic T-wave in Derivation I and preponderance of the left ventricle. At necropsy there was marked sclerosis of the terminal coronary arteries. The aorta revealed an advanced degree of sclerosis with atheromatous ulcers. The pulmonary artery was markedly sclerosed. The heart weighed 400 gm.

Case XIV (A380262).—A man, aged sixty-eight years, with the progressive myocardial failure type of disease, died from arteriosclerotic gangrene of the left foot. The electrocardiogram revealed auricular fibrillation and preponderance of the left ventricle. At necropsy the coronary arteries were markedly thickened, the left being almost occluded. The intima of the aorta throughout its entire length, especially on its posterior surface, showed many areas of thickening with some calcareous changes. There was considerable hypertrophy of the myocardium with fibrosis. A ball thrombus was found in the left auricle and there was a mural thrombosis in the appendage of the right auricle. The heart weighed 400 gm.

Case XV (A323864).—A woman, aged sixty-nine years, with the progressive myocardial failure type of disease, died from bronchopneumonia and myocardial failure following thyroidectomy for adenomatous goiter with hyperthyroidism. The electrocardiogram revealed sinus tachycardia and preponderance of the left ventricle. At necropsy the coronary arteries were found to be markedly sclerotic, but there was no obliteration. The vessels were slightly dilated. The aorta and its large branches were very sclerotic, slightly dilated, and had areas of ulceration, particularly in the arch and below the celiac axis. The endocardium of the left ventricle was thickened and somewhat opaque, while the rings of the aortic and mitral valves showed numerous patches of yellow thickening. There were a slight degree of hypertrophy and dilatation of

the ventricles, and a moderate degree of fibrosis. The heart weighed 375 gm.

Case XVI (A327933).—A man, aged sixty-two years, with angina pectoris, died suddenly. The electrocardiogram revealed sinus rhythm and T-wave negativity in Derivation I. At necropsy a moderate degree of sclerosis of the coronary arteries was noted. On the root of the aorta and on the aortic and mitral valves were areas of yellow thickening. Only a slight increase in the connective tissue of the myocardium was noted. The heart weighed 550 gm.

Case XVII (A167754).—A man, aged sixty-one years, with the progressive myocardial failure type of disease, died from cerebral hemorrhage. The electrocardiogram revealed auricular fibrillation, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy many raised yellowish plaques of thickening in the intima of the coronary arteries and a few similar changes in the root of the aorta were noted. There was a slight diffuse fibrosis of the myocardium associated with a diffuse increase of fat. Hypertrophy was marked and dilatation was moderate.

Case XVIII (A192039).—A man, aged sixty-one years, with angina pectoris and the myocardial failure type of disease, died suddenly. The electrocardiogram revealed premature contractions of ventricular origin, T-wave negativity in all derivations, and preponderance of the left ventricle. At necropsy, numerous whitish areas of fatty and fibrous changes were noted in the intima of the coronary arteries, and similar areas in the aorta and the mitral valve. The heart was enormously enlarged and the myocardium revealed diffuse fatty degenerative changes.

Case XIX (A294006).—A man, aged sixty-four years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm and T-wave negativity in combined Derivations II and III. At necropsy a moderate degree of sclerosis of the coronary arteries was noted. The aorta revealed moderate fatty and fibrous changes. Brown atrophy of the myocardium was quite marked, and there was a moderate degree of fibrosis. The mitral valves were definitely sclerotic.

Case XX (A70066).—A man, aged sixty-two years, with the progressive myocardial failure type of disease, with severe paroxysms of tachycardia, committed suicide. The electrocardiogram revealed ventricular tachycardia. At necropsy there was revealed a slight degree of sclerosis of the right coronary artery, with considerably more involvement of the left, particularly its descending branch. The aortic arch was slightly atheromatous. A few areas of fibrosis were scattered through the myocardium. The mitral and tricuspid valves were thickened and the aortic valves, besides being thickened, were slightly atheromatous.

Case XXI (A412224).—A man, aged seventy-four years, with

angina pectoris and the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed sinus rhythm, T-wave negativity in Derivation I, and preponderance of the left ventricle. At necropsy the coronary arteries were extremely sclerotic, being almost completely obliterated by endarteritis. The aorta likewise was markedly sclerotic. The muscle fibers of the myocardium were hypertrophic and hazy. The ventricles were moderately hypertrophied but markedly dilated. There were mural thromboses in both ventricles. The heart weighed 725 gm.

Case XXII (A390697).—A man, aged seventy years, with the progressive myocardial failure type of disease, died from uremia associated with pyelonephritis and carcinoma of the prostate. The electrocardiogram revealed sinus tachycardia, negative P-wave in Derivation III, and preponderance of the left ventricle. At necropsy the left coronary artery was markedly sclerosed and almost totally obliterated, while the right coronary artery was enormously dilated. The aorta was markedly sclerotic, and there were marked fragmentation and segmentation of the muscle fibers of the myocardium. The aortic cusps were sclerotic along their line of attachment, and there was fenestration of all the cusps. The heart weighed 450 gm.

Case XXIII (A386550).—A man, aged seventy-one years, with the occult coronary type of disease, died from pyelonephritis and pneumonia following prostatectomy. The electrocardiogram revealed premature contractions of auricular origin, and preponderance of the right ventricle. At necropsy the coronary arteries were markedly sclerotic, but were not occluded. Over the posterior surface of the aorta were several raised yellow plaques varying in size; two in the descending aorta were ulcerated and showed calcareous changes. The margin of the left aortic cusp was fenestrated. Slight segmentation and fatty replacement of the myocardium were noted around some of the bloodvessels. The heart weighed 245 gm.

Case XXIV (A353997).—A man, aged seventy-eight years, with the progressive myocardial failure type of disease, died suddenly. The electrocardiogram revealed premature contractions of auricular origin, diphasic T-wave in Derivation I, and preponderance of the left ventricle. At necropsy marked arteriosclerosis of the coronary arteries with calcification was noted. The aorta was markedly sclerotic with raised plaques and areas of calcification; ulceration was most evident at the juncture of the larger vessels. The aortic endocardium was sclerotic and there was considerable aortic stenosis. There was marked sclerosis of the iliac arteries. The myocardium revealed degenerative changes and was hypertrophied.

Case XXV (A84930).—A man, aged seventy-one years, with the progressive myocardial failure type of disease, died from gradual cardiac failure. The electrocardiogram revealed premature con-

tractions of auricular and ventricular origin and preponderance of the left ventricle. At necropsy the intima of the coronary arteries revealed small, yellow, tabular plaques of thickening. The aorta was similarly involved, some of the areas showing ulceration and calcification. There was a moderate increase in the fibrous tissue of the myocardium between the muscle bundles, which varied in size and appeared granular on cut section. There was a moderate degree of hypertrophy and dilatation. The heart weighed 475 gm.

Discussion of Electrocardiograms. Seventeen of the cases (68 per cent), in which electrocardiographic examination was made, disclosed significant graphic abnormalities, as follows: (1) significant T-wave negativity in isolated and combined derivations in 12 cases, (2) auricular fibrillation with significant T-wave negativity in 2 cases, (3) uncomplicated auricular fibrillation in 1 case, (4) auricular flutter in 1, and (5) ventricular tachycardia in 1. It is significant that in 14 of the cases (82 per cent) in which there were important graphic abnormalities, there was significant T-wave negativity in the electrocardiograms. These, in order of frequency were: (1) T-wave negativity in Derivation I in 8 cases, (2) T-wave negativity in combined Derivations I, II, and III in 2 cases, (3) diphasic T-wave in Derivations I alone in 2 cases, (4) T-wave negativity in combined Derivations I and II in 1 case, and (5) T-wave negativity in combined Derivations II and III in 1 case. The high incidence of T-wave negativity in Derivation I alone is significant, and the occurrence of this abnormality should always direct attention to disease of the coronary arteries.

The question arises why there were no significant abnormalities in the electrocardiograms in 8 of the cases (32 per cent). Both gross and histologic study of the heart reveals only structural or anatomic changes, and affords little or no data with regard to disturbances in the physiologic processes. A critical study of Gross' work dealing with the coronary circulation, aids materially in correlating anatomic changes and the resultant disturbances in cardiac function. By the injection of opaque mediums into the coronary tree, Gross was able to produce remarkable roentgenograms of the arterial system of the heart. His specimens were all presumably normal, and averages in the various decades of life were studied comparatively and tabulated. Gross' work revealed two fundamental facts: (1) that with increasing age the anastomosis between the various branches of the coronary arteries was greater, and (2) that a definite metamorphosis occurred in the degree of vascular elements in the right and in the left side of the heart, definitely progressive according to decade. In the heart of the newborn a marked increase in the vascular elements of the right side of the heart over the left was evident; this diminished slightly, but remained dominant through the third decade of life. In the fourth decade the number and extent of the vascular elements of the left side become dominant and increase as the later

decades of life are approached; at this stage of Gross' specimens a remarkable diminution in the coronary branches of the right side of the heart occurs.

The progressive character in the diminution of the vascular elements of the right side of the heart in presumably normal specimens with the advent of age, and the marked degree which this reduced vascularity attains, are so striking that they may explain many obscure and apparent discrepancies between the gross structure of the human heart and clinical disturbances in its function. We must agree that our present methods do not permit a coördinated histologic study of the vascular structures of the heart. The nearest approach to a solution of this problem is the examination of the entire heart by serial section. This method is not only difficult, but extremely tedious, and precludes the study of large numbers of specimens. No coördinated study in a representative series of cases of the coronary tree in its entirety, in relationship to functional disturbances of the heart and studies in electrocardiography, has been made to our knowledge.

After a careful study of the reproductions of Gross' specimens, particularly of those of patients in the later decades of life, in which the blood supply of the right side is so definitely reduced, one can readily picture the condition that might exist with sclerosis of the coronary arteries. Assuming that the blood supply of the right side of the heart in older persons is already reduced, the further reduction from a superimposed sclerosis of these arteries could readily lead to a degree of avascularity, resulting in variable functional cardiac disturbances and in variable degrees of degenerative myocardial changes. The myocardial effects of coronary sclerosis are probably largely determined by the degree of anastomosis between the arterial branches, which varies even in the normal heart. With these observations in mind, the occurrence of normal electrocardiograms in certain patients with coronary sclerosis finds a tentative explanation at least.

Pardee and Master recently reported 11 cases of cardiac disease in which a correlation between clinical types, electrocardiographic findings, and necropsy data had been made. They found the coronary arteries diseased in all but 1 case. The anterior descending branch in 1 case was occluded by a thrombus, and considerable occlusion occurred in 2 other cases. In 6 cases (55 per cent) showing disease of the coronary arteries, the electrocardiograms revealed significant T-wave negativity, in order of frequency as follows: (1) in combined Derivations I and II in 3 cases, (2) in combined Derivations II and III in 2 cases, and (3) in Derivations I alone, in 1 case. In 2 cases there was T-wave negativity in all derivations, which was attributed to the administration of digitalis. These authors apparently regard these graphic abnormalities as of very little importance. The question is curtly dismissed by, "These various types of electro-

cardiographic abnormality have been considered to be associated with abnormality of the ventricular muscle, but the evidence for this is only of circumstantial character."

We have repeatedly studied large groups of cases in which there was significant T-wave negativity in the electrocardiograms, and have repeatedly called attention to the high cardiac mortality attending these disorders.[10, 13] Our results have recently been confirmed by MacIlwaine and Campbell, who found even higher mortality averages. We believe that the accumulated data regarding the importance of significant T-wave negativity as indicative of serious myocardial disturbances has attained a position where evidence supporting its value can hardly be referred to as circumstantial.

Summary. The average age of the patients was sixty and three-tenths years; the youngest was thirty-three, and the oldest eighty-one. There were 67 males (78 per cent) and 19 females (22 per cent). The symptoms were arbitrarily classified as: (1) typical angina pectoris, 21 cases (24 per cent), (2) atypical angina pectoris, 2 cases (2 per cent), (3) the syndrome of progressive myocardial failure unassociated with painful attacks, 22 cases (26 per cent), (4) the syndrome of progressive myocardial failure and typical angina pectoris, 7 cases (8 per cent), and (5) the occult type of coronary sclerosis in which insufficient subjective or objective evidence of cardiac disease existed to permit its clinical identification, 34 cases (40 per cent).

The degree and extent of sclerosis of the coronary arteries in relation to the clinical types is discussed with special reference to vessel occlusion resulting from sclerosis, thrombosis and embolism.

The aorta was found diseased in all but 1 case; it was syphilitic in 8 cases (9 per cent). There was aneurysm in 3 cases: in 2 cases involving the thoracic aorta, and in 1, the abdominal aorta.

The heart valves were diseased in 44 cases (51 per cent), and the pulmonary artery in 4 (5 per cent). In all cases there were degenerative myocardial changes. Associated disease of the pericardium occurred in 8 cases (9 per cent). Peripheral arteriosclerosis was noted in 60 cases (70 per cent), renal arteriosclerosis in 32 cases (37 per cent), and cerebral arteriosclerosis in 13 of the 15 brains examined. Forty-six patients (53 per cent) had had varying degrees of nephritis. The gall-bladder had been diseased in 22 cases (26 per cent).

Twenty-seven patients (31 per cent) had had hypertension; the average readings were systolic 183, diastolic 111, and pulse pressure 72. Fourteen patients (16 per cent) had had hypotension. Fourteen (29 per cent) of 49 patients, whose height and weight were recorded, were obese.

Sudden death occurred in 32 cases (37 per cent), in order of frequency in the clinical groups as follows: typical angina pectoris in

12 cases (38 per cent), occult coronary type in 7 cases (21 per cent), angina pectoris with progressive myocardial failure type in 6 cases (19 per cent), progressive myocardial failure type in 5 cases (16 per cent), and atypical angina pectoris in 2 cases (6 per cent).

Gradual cardiac failure occurred in 13 cases (15 per cent). The incidence according to clinical types was: (1) angina pectoris in 5 cases (38 per cent), (2) progressive myocardial failure type in 5 cases (38 per cent), (3) occult coronary disease in 2 cases (15 per cent), and (4) angina pectoris with progressive myocardial failure type in 1 case (8 per cent).

Death following surgical operation resulted from various causes in 21 cases (24 per cent), but in only 1 was it attributable to cardiac disease.

Death was due to other causes in 22 cases (23 per cent).

Twenty-five patients (29 per cent) had had electrocardiographic examination, 17 of whom (68 per cent) had revealed significant graphic abnormalities. These findings were: (1) significant T-wave negativity in isolated and combined derivations in 12 cases, (2) auricular fibrillation with significant T-wave negativity in 2 cases, (3) uncomplicated auricular fibrillation in 1 case, (4) auricular flutter in 1 case, and (5) ventricular tachycardia in 1 case.

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CORONARY ARTERIAL OCCLUSION: A PERFECTLY DEFINITE SYMPTOM-COMPLEX; THE REPORT OF THIRTEEN CASES WITH ONE AUTOPSY.

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Coronary arterial occlusion with cardiac infarction has until recently been recognized only as a pathological curiosity at the autopsy table. It is only during the past decade or two, through the results of careful physiological experimentation and clinico-pathological observations, that a definite complex of symptoms have been portrayed characteristic of occlusion of these arteries. The cases herein recorded, 13 in number, have been carefully studied, and each one found to present the subjective symptoms and physical signs considered diagnostic of this clinical entity. Of the 5 fatal cases but 1 came to autopsy. This case showed a definite thrombosis of a large descending branch of the left coronary artery with a fresh cardiac infarct.

The coronary arteries, although considered physiological end-arteries, communicate, especially their smaller branches, in a most remarkable mesh of fine arterioles and capillaries. This very free anastomosis has been beautifully demonstrated by Gross, Baldwin, Jamin, Merkel, Ordway, Hirsch and Spalteholtz and others from the study of stereoscopical roentgen-ray photographs taken from carefully prepared and injected coronary vessels of man and animals.

The experimental occlusion of the coronary arteries in animals by Porter, in 1893, showed that when the main coronary arteries were plugged sudden death in all animals occurred; whereas, when the circumflex vessels were occluded death occurred in 10 per cent, and in only 50 per cent of the animals when the large descending branches were involved. Death as a result of the occlusion of these large branches was instantaneous or in a few hours or days, death often being preceded by auricular or ventricular fibrillation.

Porter's experiments seemed to show that the results of such operations varied according to the amount of myocardium deprived of its blood supply. When the smaller arteries alone were occluded, such as the arteria septi and the small descending branches, the heart was not seriously affected.

The pathological changes most frequently found associated with occlusion of the coronary arteries, apart from the infarcted area of the myocardium and the subsequent changes resulting therefrom, are atheromatous changes of the presigmoid part of the aortic arch, including the sinuses of Valsalva and mouths of the coronaries. Similar changes in the coronary arteries, aneurysm of the thoracic aorta, infectious and syphilitic mesaortitis, syphilitic

endarteritis, obliterating arteritis, general arteriosclerosis, chronic pericardial adhesions and myocardial degeneration. Sudden embolic plugging may occur in septicemia and pyemia or during the course of septic or simple endocarditis or from the disentanglement of mural thrombi from the cardiac chambers, and especially may they be detached from the musculi pectinati of the auricular appendages.

As a result of the plugging of a branch of a coronary artery by a thrombus or embolus, there occurs an anemic infarct with an area, small or large, of myomalacia. If this area is small it goes on to repair by connective-tissue substitution or fibrosis, leaving a small area of scar tissue which does not, save transiently, impair the myocardial function. If, on the other hand, a large area of softening occurs from the plugging of a large branch, permanent and very serious myocardial insufficiency may result, or aneurysmal dilatation of the ventricular wall may occur, or a true ventricular aneurysm appear with early rupture, or ventricular puncture may occur with, in both instances, sudden death from hemopericardium.

The symptoms of thrombosis of the coronary arteries are quite characteristic and form a definite group or complex easy of recognition and pathognomonic of this condition.

For the recognition clinically of thrombosis of the coronary arteries and the presentation of this characteristic syndrome we are especially indebted to the studies of Sir William Osler, George Dock, Sir Clifford Allbutt, Krehl, Sternberg, Whitington Gorham, Libman, and Herrick and his co-workers. This complex consists of the following important symptoms, many of which are abrupt in their onset.

Pain.—Sudden excruciating anginoid pain, substernal (angina pectoris) or upper abdominal (angina abdominalis) in character, with or without the characteristic radiation of true angina pectoris.

The pain is usually of great severity and if the patient, as so frequently happens, has been subject to previous attacks of angina pectoris, he will state that the pain of this attack is much more atrocious than that of any previous one. The pain in most cases continues unabated for several hours or days "status anginosus," or rarely it may be but transient or it may recur at short intervals.

As stated above, the pain not so infrequently takes its origin or is referred to the upper abdomen, and because it is often associated with vomiting, gaseous distention and upper recti muscle spasm it has often been mistaken for an acute inflammatory condition of the abdomen, such as an appendix or gall-bladder, perforation of a gastric or duodenal ulcer, hemorrhagic pancreatitis or a sudden intestinal block, and in consequence therefore of such error some of these sufferers have been subjected to unwise and needless surgical intervention.

Facies. The facial expression is one of great anxiety, the color is pale, leaden or ashen gray; the skin is cold and bedewed with sweat; the features are pinched and the expression indicative of great pain, shock and extreme exhaustion; recurring fainting attacks may occur on the slightest exertion, while that curious mental phenomenon angor animi, or feeling of immediate dissolution, is rather common.

In most all cases (all but 3 of this series) an acute emphysematous distention of the thorax suddenly appears, and this condition is usually associated with great dyspnea, which may amount to extreme orthopnea, with variable degrees of cyanosis and moist crackling rales from passive hyperemia, and edema of the bases of the lungs. Extensive pulmonary edema was present at the onset in 10 of the cases herein recorded, and extreme air-hunger was a noteworthy symptom in all but 2 of the cases.

Pulse. The pulse is often rapid, easily compressed and thready; in many cases it soon becomes grossly irregular. The vessel wall is usually found thickened, although in 3 of my cases both the radial and temporal arteries were palpably normal. The systolic blood-pressure in most cases suddenly falls, while the diastolic is usually sustained and the pulse pressure correspondingly narrowed. This sudden drop in the systolic blood-pressure has been observed in such a large number of cases that, taken with the other symptoms, it may be justly regarded as of considerable diagnostic value.

Heart. The cardiac impulse is often a diffuse feeble tap, or it is not visible or palpable. The heart sounds are distant, the action usually tumultuously irregular and a gallop or tic-tac rhythm is rather frequently observed. Auricular fibrillation is, perhaps, the most commonly observed type of arrhythmia, and is of diagnostic significance if occurring for the first time with the above described symptoms. Pulsus alternans, acute auricular flutter, repeated extrasystoles, auriculoventricular and arborization block are not infrequently found; paroxysmal tachycardia of ventricular origin has also been observed in a few cases, most of which have been fatal. Acute dilatation of the heart is common and may be recognized by a sudden increase in its transverse diameter, both to the right and left, and distant feeble heart sounds, a gallop or tic-tac rhythm, associated with the sudden onset of the symptoms of myocardial insufficiency.

Pericardial Friction. By far the most characteristic diagnostic sign, if not absolutely pathognomonic of this symptom-complex is, as so well described by Gorham, the presence of a strictly localized, evanescent, to-and-fro pericardial friction rub, due to a roughening of the pericardial surfaces from a fibrinous exudate overlying the area of the myocardial infarct and appearing within a few hours, or a day or two or three after the abrupt onset of myocardial insufficiency. The pericardial rub is often difficult to

detect and must be most conscientiously sought for at each visit, otherwise it may be entirely overlooked. Gorham found it present in 5 of his 6 cases reported in the *Albany Medical Annals* for April, 1920. He believes that in the 1 case its absence may be explained by the fact that the infarcted area was on the posterior aspect of the left ventricle and a hemopericardium had developed. It was present in 11 of the 13 cases herein reported and may have been present early in 1 case, as the patient was seen some two weeks after the original insult, and he assured me that his heart had not been examined.

In most cases a fever of a mild type develops and lasts for a few days to a week. It is usually associated with a slight or moderate polymorphonuclear leukocytosis. Both of these symptoms may result from protein absorption from the softened infarcted area. While the failure to detect or the absence of a pericardial friction rub does not invalidate the diagnosis of coronary artery occlusion, its presence, particularly if associated with the above described symptoms of acute myocardial insufficiency, is of great diagnostic significance and serves to make the diagnosis positive.

Electrocardiographical Changes. R. Herrick has recently shown from a clinical study of several cases of thrombosis of the coronary arteries that the T-wave is inverted in leads I and II of the electrocardiogram and that evidence of arborization block is not infrequently found.

His colleague, Smith, has confirmed these results experimentally in animals by ligation of the descending branches of the left coronary artery. The experiment showed an immediate exaggeration of T-wave and its return within twenty-four hours to negativity, to be followed later to its positive position and then to return to a final iso-electric or negative position. These changes were not noted when the right circumflex branches were so operated. Herrick and Smith believe that the above described electrocardiographical changes are diagnostic of coronary artery occlusion in man and animals.

Morris Kahn states that this change of the T-wave from a strongly positive peak to a markedly negative one, and then a slow return to the positive or iso-electric form, is so characteristic experimentally that similar changes in this wave in man may reasonably be supposed to be due to similar lesions in the left coronary artery. Ventricular paroxysmal tachycardia has been observed by Robinson and Hermann in 4 cases clinically of occlusion of the coronary arteries, in 1 of which a fresh thrombus was found at autopsy.

Four types of cases of coronary artery occlusion are observed:

1. Cases, not at all rare, where death is very sudden, preceded or not by terrific substernal pain. Autopsy only discloses the true nature of the condition.

2. Cases which are preceded by the above described subjective

symptoms and physical signs of coronary artery occlusion, death occurring suddenly or in a few hours or days.

3. Cases in which death is due to myocardial insufficiency weeks or months after the characteristic abrupt stormy onset.

4. Cases, 8 in this series, with abrupt onset with all the clinical manifestations of this entity, which eventually make a fairly good recovery but with a diminished cardiac reserve.

Case Reports. CASE I.—Angina pectoris; sudden death; thrombosis of a descending branch of the left coronary artery with a fresh cardiac infarct; no pericardial friction rub audible. (Autopsy.)

H. F. L., aged seventy-three years, a farmer, entered the Mary McClellan Hospital, March 21, 1920, complaining of shortness of breath and substernal pain.

History. The family history was without import save that his father and mother lived to be very old and died of senility. He had had the usual childhood diseases since which time until the onset of the present illness he always enjoyed good health.

The present illness began about two weeks ago, when following the drinking of a large quantity of cider he became very nauseated; he vomited several times and a severe diarrhea ensued. The evening of the day in which this digestive upset occurred he became extremely short of breath and had to sit up in bed all night. At first he had a dry unproductive cough, which later became quite loose. At the same time he experienced a dull but rather severe pain in the region of the middle of the chest which did not radiate. He had no edema of the limbs, trunk or face.

Physical Examination. He was fairly well nourished; his facial expression was anxious and he was quite pale. There was no edema and his respirations were hurried. He was propped up in bed and suffered with dyspnea. His cranial nerves were intact, with the exception that the pupils did not react to light either direct or consensually, and an external strabismus of the left eye existed. The eye-grounds showed definite evidences of arteriosclerosis. The chest was emphysematous in type. The lungs were hyperresonant throughout. This vesiculotympanitic note obscured both the cardiac and upper liver dulness. The expiration was prolonged and low in pitch in the clavicular regions. There were a few moist crackling rales at the bases.

Heart: The cardiac impulse was not visible or palpable; a distinct diffuse epigastric pulsation was present. The heart sounds were feeble and distant. The aortic second sound was louder than the pulmonic. There was no endocardial or exocardial murmurs. The pulse-rate was 86; it is regular but feeble; the vessel wall was very much thickened. The cardiac area could not be made out because of the hyperresonant note.

The liver could not be palpated. There was no tenderness in the region of the gall-bladder; it could not be palpated.

The abdomen was not distended; no muscle spasm existed; no evidence of free fluid, splash, tumor mass or herniæ.

The spleen could not be outlined either by percussion or palpation. The extremities were free; motion and sensation were intact; the reflexes were normal.

Course. There was a slight rise of temperature during his stay in the hospital. Urinalysis showed nothing abnormal. The patient seemed gradually to improve each day until March 29, when, while talking to a patient in an adjoining bed, he suddenly became very cyanosed and expired.

Autopsy showed very marked sclerosis of both coronary arteries, with a fresh thrombus in one of the descending branches of the left coronary artery and in the left ventricular wall, near the apex, an area of softening about 4 cm. wide. This recent infarct was thinned, velvety and red in color. The lungs were very emphysematous but otherwise normal. The pulmonary artery was not thrombosed. The gall-bladder contained a number of gall stones.

In this case the pericardial friction was missed, doubtless because the original attack of angina occurred two weeks before he entered the hospital, and the chest had not then been examined.

Case II.—Chronic myocarditis; angina pectoris; coronary artery occlusion; acute cardiac decompensation. (Recovery.)

Mrs. I. H. H., aged fifty-two years, was admitted to the Mary McClellan Hospital, June 28, 1920, complaining of precordial pain, cough, dyspnea and great weakness.

History. Her family history was without import. She had been a sufferer for four years with diabetes mellitus, otherwise she had had no illness since childhood. She has one living child; no still-born or miscarriages.

The present illness had begun three days before, with a severe pain in the region of the sternum which came on suddenly; it lasted but a few minutes, only to be repeated six hours later with great severity and with the sense of intense substernal pressure. This pain and pressure discomfort disappeared the following morning.

Examination. A woman of medium build; was slightly cyanotic, very dyspneic, with anxious facial expression, ashen color, but with no edema. The lungs were hyperresonant; fine moist rales were present at the bases.

Heart: Distinct tenderness on pressure existed over the precordial region. The cardiac dulness at the level of the fourth rib was increased to the left to the mid-clavicular line and to the right 1 cm of the sternal margin. The heart sounds could be only feebly heard. There was a definite gallop rhythm; no friction or endocardial murmurs were present.

Course. June 29 a definite rough pericardial friction rub at the junction of the third left costal cartilage with the sternum was heard, localized to an area the size of a silver quarter of a dollar, and increased in intensity by the pressure of the chest-piece of the stethoscope, which also brought out tenderness and excited pain. The pulse was irregular, rapid and compressible. The blood-pressure was 110/80 mm.

On July 3 the patient seemed better; there was no dyspnea, cyanosis or edema. The pericardial friction was distinct; the pulse was regular; the blood-pressure 115/80 mm. She complained of mild substernal pain, extending out to the left axilla.

July 26 the patient was in bed. Respirations were normal; color, pink; rhythm, regular; heart sounds, clear but distant; no friction; no constriction or precordial pain or uneasiness.

She was discharged, August 10, 1920. During her stay in the hospital sugar and casts were constantly found in the urine. Her temperature ranged from 99° to 101° F. for a period of three weeks.

December 24, 1922, she was still alive and was able to do light housework and exercise moderately without much discomfort.

CASE III.—Occlusion of a coronary artery with sudden death. (No autopsy.)

Mr. F. E., aged sixty-eight years, was seen in consultation with Dr. Otis Z. Bouton, of Fultonville, N. Y., on September 18, 1918.

History. Four brothers died of angina pectoris. One died after the onset of a very severe attack of substernal pain; one died two weeks after recurring attacks of angina pectoris, "coronary thrombosis." The other two brothers had been sufferers from angina and both died suddenly.

The patient had always been well until January 26, 1916, when, following a severe cold, he developed acute hemorrhagic nephritis, from which he apparently made an excellent recovery.

April 15 he was treated for a severe attack of influenza, which confined him to bed about ten days.

August 23 Dr. Bouton received an urgent call, and found the patient with an anxious expression, pale, bedewed with sweat and complaining of a squeezing, crushing pain beneath the sternum, running down the left arm to the little and ring fingers. He stated that for the past few weeks the slightest exertion had brought on similar, though much milder attacks. He was relieved by glonoin and morphin. His blood-pressure was not taken. His pulse was regular and not accelerated.

August 28 he went to the doctor's office and expressed himself as feeling better, but was very weak. His blood-pressure was 100/80 mm.; the heart sounds were weak; a soft systolic apical murmur was heard.

On September 3 he had another attack of substernal pain, not as

severe as the first attack, but followed by great prostration, considerable dyspnea, anxious, pinched facies and cyanosis.

I saw him two days later and found him semi-erect in bed, with respirations quickened and shallow, lips and fingers blue, with slight soft edema about the tibiæ and ankles. The pulse was 110, very irregular and thready; vessel walls were thickened; the heart's impulse was feeble and diffuse, its action tumultuous and a soft systolic mitral murmur and a very typical to-and-fro superficial pericardial friction sound were heard just within the site of the impulse, covering an area about 2 cm. in diameter. The heart sounds were distant. The cardiac dulness extended 10.5 cm. to the left of the mid-sternal line and 3 cm. to the right. The blood-pressure was 90/70 mm.

The lungs were hyperresonant throughout, and numerous bubbling subcrepitant rales were present at the bases. His temperature was 97.8; no cell count was made. The urine contained a trace of albumin.

The patient continued as above described until September 12, 1918, when he had another attack of substernal pain, and died before the doctor could reach him. A postmortem examination was not allowed.

This case is of particular interest because of the fact that four brothers died of what had been diagnosed as attacks of angina pectoris—three suddenly, shortly after the onset of angina pectoris, and one two weeks after recurring attacks of angina, probably of coronary arterial thrombosis.

Case IV.—Thrombosis of a coronary artery with the rapid onset of acute heart failure and death. (No autopsy.)

The patient was a male, aged forty-eight years, of French descent, a mill-worker; he was married, with wife living, and the father of four healthy children. He denied venereal disease. His habits were excellent; he used neither tobacco or alcohol.

History. In the autumn of 1922, while undergoing an examination for a life insurance, it was found that his systolic blood-pressure was 240 mm. He had, however, no cardiac embarrassment; in fact, he appeared and felt in excellent health.

March 9, 1923, while returning home from work, he stopped at the office of his physician, because of severe pain in the mid-epigastric region, which became most agonizing, and he felt as if he would die; the pain radiated to the left shoulder.

The doctor stated that his features were pinched, that he was blanched and appeared like one suffering from great shock. For a few seconds he could not palpate the pulse at the wrist. He gave him stimulants and a hypodermic of morphin and atropin and several doses of nitroglycerin.

In the course of an hour his pain was some improved and the

doctor took him to his home. His pulse was thready, rapid and irregular; the heart's action was tumultuous. The following day he still had some uneasiness in the substernal region and his chest felt sore. The breathing was rapid and short, and many moist rales existed at the lung bases.

The second day after the onset of the severe anguish the doctor discovered a rough to-and-fro superficial friction rub over the body of the sternum at about the junction of the fourth costal cartilage. This continued for two days and then became inaudible. It was noticed at this visit that the urine which he passed was bloody, but there was no pain or frequency. Shortly after the onset it was also noticed that in addition to his extreme exhaustion, breathlessness and palpitation, that his feet and ankles were swollen and this edema gradually extended upward. The hematuria soon ceased, but the quantity was greatly reduced.

On June 5 I saw the patient with Dr. S., his physician, and found him sitting upright in an arm chair, unable to lie down because of the extreme dyspnea. Soft edema of the extremities and trunk were present, his complexion was sallow and his lips, finger tips and ears violaceous. The pulse-rate was 80, and it was easily compressed and very irregular—a medley of feeble and rather strong beats; the vessel walls were thickened. The cardiac impulse was feeble and diffuse, and no thrill of friction was palpable. There was heard a soft systolic apical murmur not conducted (relative mitral insufficiency?). No pericardial friction rub. The cardiac dulness was 14 cm. to the left and 4 cm. to the right of the mid-sternal line. A pulse deficit of 50 was present, the rate at the impulse being 130. A definite gallop rhythm was present. The jugulars showed a large systolic venous movement.

The chest was voluminous and physical signs of a hydrothorax were present, more marked on the right side.

The abdomen was distended in its upper half, due to the pressure of an enlarged smooth tender liver which reached downward almost to the level of the umbilicus. The spleen could not be palpated or outlined by percussion.

He had for two weeks or more after the onset of the attack a mild fever which ranged from 99° to 101° F. A leukocyte count, made during the second week of the illness, showed a leukocytosis of 13,000.

He died four days after my visit from the extreme cardiac insufficiency. No postmortem examination could be obtained.

Case V.—Thrombosis of a coronary artery. (No autopsy.)

The following case was seen in consultation in July, 1917, at Arlington, Vt. Mr. D., aged sixty-two years, a railroad man, had for about two years been the subject of mild attacks of angina pectoris, manifested by pain of a constricting-like character, sub-

sternal in location and referred to the left shoulder and down the left arm in the ulnar distribution. He had been under a New York physician's care for hypertension and an enlarged heart.

Four days previous to my visit he was suddenly seized shortly after returning from a long automobile trip, he having driven his own car, with most excruciating substernal pain, great pallor and sensation of impending dissolution, which was only partially relieved by repeated doses of nitroglycerin and 0.5 gr. morphin hypodermically. Two days later, having in the interim suffered no precordial anxiety, he was taken with another similar attack to the above, although milder in character. Soon thereafter he became very dyspneic, was cyanosed, very nervous and restless and unable to sleep. His facial expression was pinched and he was very pale, with lips violaceous. His pulse, which before had been regular and slow at the rate of 68, with a systolic blood-pressure registering 190 mm., was now rapid and very irregular; his systolic pressure had dropped to 110 and his diastolic to 70. His heart action was tumultuous, and a soft systolic murmur was heard at the apex and faintly conducted to the left ("relative incompetency"). Many large subcrepitant rales were heard at the base posteriorly. My opinion was that following the onset of the second attack of angina pectoris a large branch of one of his coronary arteries became plugged with a thrombus and, accordingly, I gave a very grave prognosis.

I saw him two days later and found him in extremis with all the above-mentioned symptoms, greatly exaggerated, and, in addition, a localized fresh pericardial friction rub about 3 cm. in diameter, and heard best over the body of the right ventricle at the junction of the fourth costal cartilage with the sternum. He died the following day, and despite our entreaties no postmortem examination was allowed.

The interesting features of this case were the sudden onset, following a very severe anginoid attack, of grave myocardial insufficiency and auricular fibrillation, sudden fall of systolic blood-pressure, development of relative mitral incompetency and the sudden appearance of a transient localized pericardial friction rub.

Case VI.—Thrombosis of a coronary artery with partial recovery; temporary loss of consciousness and disappearance of pulse at the wrist; localized bulging of heart shadow (roentgen-ray).

Mr. F. L., aged sixty-eight years, was a farmer by occupation.

History. His family history was without import. He had always been well since childhood, save that twelve years before he developed dizzy attacks, and it was then noted that his blood-pressure was high. Otherwise he had been very well and active on his farm.

The present illness began suddenly, June 28, 1922, when he

became very sick on his way to work in the fields. No acute pain was felt, but a feeling of sudden exhaustion and an inability to continue, with precordial distress and a numbness extending down the left arm and hand. When questioned closely he stated that there was no actual pain, just a numbness. This attack was accompanied with vomiting and a loose bowel movement. He was assisted to his home and laid on a couch, when he became very cyanosed and dyspneic and immediately lost consciousness. A physician was called and found him unconscious, very cyanosed and pulseless. Strychnin and nitroglycerin were administered and shortly afterward he improved. The pulse became palpable, with a rate of 40 per minute, but irregular in rhythm and volume (heart-block). He regained consciousness in a few seconds, and then complained bitterly of precordial distress, which was only partially relieved with 0.25 gr. morphin.

The next day his pulse-rate was 90; his temperature was 100° F. The day after this his pain was very much less; his pulse was very irregular and 140 per minute, weak and thready. The blood-pressure was 120/80 mm. His systolic pressure had previously been between 180 and 160 mm.

For a few hours only, on the third day following the attack, there was a pericardial friction rub heard over a small area to the left of the sternum near the junction of the left fourth costal cartilage. Improvement was very gradual for two weeks when there occurred a relapse, the pulse-rate reaching as high as 130, with periods of arrhythmia, extrasystoles and clinical alternation. This lasted about four days, when he suddenly improved, the pulse-rate not rising above 100 and quite regular.

At the present time, ten weeks after the onset of the trouble, the patient is up and about and feeling fairly well. He is quite dyspneic on exertion. The pulse remains about 90 and is, with the exception of extrasystoles, regular.

Fluroscopical examination and roentgen-ray pictures show a well-defined localized bulging, apparently an aneurysmal dilatation, of the wall of the left ventricle at about its middle-third, the size of a small tangerine, or possibly a large dilated left auricle.

Case VII.—Coronary artery thrombosis with sudden death. (No autopsy.)

W. A. B., aged fifty-six years, on April 21, 1921, had a severe crushing-like pain in the lower sternal and upper abdominal regions, which at first was thought to be due to an attack of indigestion or gall-bladder implication. This condition was suddenly followed by marked clinical evidences of myocardial insufficiency.

History. The family history was without import. He had always enjoyed good health, was a strenuous worker and had large business interests to occupy his attention.

When I saw him two days later, with Dr. Henning, the examination disclosed a well-nourished man with anxious facial expression, pale and ashen. The respirations were hurried and he evidently suffered from marked air-hunger. The pulse was rapid and very irregular. The cardiac impulse could not be seen or palpated. The heart sounds were clear but distant, the action tumultuous and numerous extrasystoles were easily recognized. The lungs were hyperresonant, except at the bases, which were dull, and many fine moist rales were present. There was soft edema of the feet and ankles. The blood-pressure was 135/110 mm. He was exceedingly nervous, and still complained of a continuous substernal pain of a dull character. So great was his distress that he was unable to rest in bed. Waves of dyspnea often appeared, accompanied with marked cyanosis.

From the above-described symptoms I made a probable diagnosis of coronary artery thrombosis, and advised Dr. Gow, the attending physician, to watch closely for the onset of a localized pericardial friction rub. I have, therefore, incorporated the notes contained in his recent letter to me.

I saw the patient, April 23, at which time he was unable to lie down and complained bitterly of severe substernal pain. The pain was only partially controlled by morphin (gr. $\frac{1}{8}$ every three hours). The heart sounds were very feeble and indistinct. There was no marked dyspnea, and at this visit no pericardial friction was heard. He remained the same for two days, when he developed a distinct pericardial friction rub over the body of the sternum near the zyphoid, which continued twenty-four hours and then disappeared. He then complained of no pain, was clear mentally and was able to lie comfortably. He seemed very weak, and stated that he was completely exhausted.

April 26 he seemed about the same, save that his pulse was very rapid.

April 27, just before death, he suddenly became unconscious and died in a few minutes. Digitalis was administered both *per* oris and hypodermically, without the slightest effect on the pulse. He evidently suffered from a thrombosis of a large branch of a coronary artery, and his death may possibly have been due to hemopericardium from a rent of the myocardial wall.

Case VIII.—Coronary artery thrombosis with recovery.

Miss M. L., aged fifty-two years.

History. Her father died of cerebral hemorrhage; her mother died of mitral stenosis. Two brothers and one sister are healthy. One sister died in infancy of an unknown cause.

She had pneumonia seven years ago and jaundice twenty years ago, and has had vague rheumatic pains in the right hip-joint. For the past several weeks she has been conscious of shortness of

breath and substernal pain on exertion. During the past three years she has had three attacks of severe neuralgic-like pain in the sternal region which did not radiate.

In the evening of April 14, 1921, she had a sudden severe attack of substernal pain, with a sensation of severe pressure, as if the sternum was being pressed inward; this discomfort was accompanied by severe air-hunger. The pain at first radiated to the left wrist and later to the right. Her breathing was so difficult that when Dr. Russell called he found her in extremis, lying with her head out of a window. She was coughing up quantities of a light foamy blood-stained fluid. The pulse was very feeble, rapid and irregular. Her color was pale and her expression very anxious; the eyes were glassy and prominent.

I saw her the next morning and made the following notes:

Examination. A large well-built female, found lying down. Her respirations were quickened, her lips cyanosed and she had a loose wheezy cough, but no edema. Her chest was voluminous and emphysematous in type. The percussion note was hyperresonant, and there were many sonorous, sibilant and fine mucus rales, with puerile breathing.

Cardiovascular system: The radial pulse was small and irregular, with a rate of 120, and of fair tension. Both temporals and radials were tortuous and thickened, and there was an occasional extra-beat. The impulse was in the fifth interspace 1 cm. to the left of the left mid-clavicular line, a diffuse feeble tap. Cardiac dulness at the fourth rib extends from 2 cm. to the right of the sternum to 1 cm. to the left of the left mid-clavicular line. The rate at the apex was 144, and a definite gallop existed. The sounds were distant and very feeble. A soft systolic apical murmur, well-conducted to the left axilla, was heard, and a to-and-fro pericardial friction rub was well heard over the body of the sternum and strictly localized. The jugulars were full and pulsating and very difficult to count. The blood-pressure was 180/120 mm.

The liver dulness extended from the fifth rib to the costal border, and no pulsation of it was felt. The spleen was not outlined by percussion or palpation. The gall-bladder was not palpable, and no tenderness was observed. Her mind was clear, but she was very nervous and apprehensive.

The urine examined by Dr. Russell was found to be normal.

A diagnosis of thrombosis of a coronary artery was made by Dr. Russell, which seemed justifiable in view of the above-described symptom and physical findings. The pericardial friction was very distinct and strictly localized to an area about 2 cm. in diameter.

A note from Dr. Russell states that the patient was confined to her bed for four weeks, when she showed marked improvement; she was then permitted to be about her room, to walk slowly on the flat, and to do light work about the house. She has remained

in fair health, although when overtired or strenuous she has precordial distress and dyspnea.

Case IX.—Thrombosis of a coronary artery with death three weeks later from myocardial insufficiency. (No autopsy.)

Mr. A., aged sixty-six years, was seen by me on September 21, 1921, in consultation with Dr. Gillen, of Cohoes, N. Y. Three days previously he had been seized suddenly at night with an excruciating pain, which was felt beneath the body of the sternum and passed directly through to the back. This pain lasted almost unabated for an hour and then was only partially relieved by a hypodermic injection of $\frac{1}{3}$ gr. of morphin. The pain gradually subsided, so that the next day he had no pain, but felt sore in the precordial region. For several months prior to the above-described attack he had noticed that on hurrying, walking against a strong wind, lifting heavily or going up stairs he felt a substernal pain and constriction of the chest. This condition had been diagnosed by the former attendant as one of indigestion.

Examination. The patient was propped up in bed with pillows. His facial expression was pinched and anxious and he was very pale. His lips were blue. The respiration was short and rapid, and he had an unproductive cough. He seemed very ill indeed. The pulse-rate was 140, very irregular and thready. The temporal and radial arteries were thickened, and he had a marked arcus senilis. The systolic pressure was 110 mm.; the diastolic pressure was 90 mm. The chest was universally vesiculotympanitic on percussion, and a number of medium-sized bubbling rales were detected at the bases both in front and back. The heart action was tumultously irregular; the impulse was a diffuse feeble tap in the fifth interspace, 0.5 cm. to the left of the left mid-clavicular line. The heart sounds were very distant. There was a slight though definite pericardial friction rub, best heard just inside of the impulse, close to the left edge of the sternum. The temperature was 100° F.

A diagnosis of thrombosis of a coronary artery was made (probably a branch of the right coronary), and in view of the physical findings of marked myocardial insufficiency a grave prognosis was given.

The patient continued the same for a period of about three weeks, when he developed edema of the extremities, marked oliguria, a very large, easily palpable and tender liver, great ascites and hydrothorax. He died suddenly a few days afterward. No post-mortem examination could be obtained.

Case X.—Thrombosis of a small branch of a coronary artery with recovery.

Dr. E. E., a practising physician, entered the Samaritan Hospital,

October 29, 1921, complaining of extreme weakness, palpitation, some dyspnea and fainting and dizzy attacks on the slightest exertion.

History. His present illness began about five weeks before, while on a visit to Washington. It followed a rather hearty breakfast, the patient being suddenly seized with a severe pain beneath the lower sternal region. He vomited several times, and the pain was so severe that he took nitroglycerin and a hypodermic of morphin, with, after a time, considerable relief; he remained in bed for ten days, during which time his temperature ranged from 99° to 101° F. He stated that directly following the onset of the attack he was extremely prostrated and nervous.

His family history was unimportant. His personal history was also without special interest. Six years ago he was operated upon for adenoma of both breasts. Two years later he suffered from a nervous breakdown, from which he made an excellent recovery.

Examination. He was well nourished, presented no edema or cyanosis and when recumbent suffered from no shortness of breath. The skin and mucous surfaces were rather pale. His facial expression was anxious.

The chest was symmetric and expanded equally; the note was a little hyperresonant, but a good vesicular murmur existed throughout; no rales were detectable.

Heart: The impulse was palpable in the fifth interspace just within the left mid clavicular line; it was a rather feeble tap. The cardiac dulness began at the upper border of the fourth rib and extended 10 cm. to the left and 2 cm. to the right of the mid-sternum. No thrill or friction was detectable. The heart sounds were clear, but distant and quite feeble. There was no marked accentuation of either the aortic or pulmonic second sound and no adventitious sounds. The substernal dulness was not well outlined. No episternal pulsation was found. There was a definite, though slight, protodiastolic gallop rhythm; immediately on sitting upright in bed or in the standing position there appeared on auscultation an extrasystole following each normal beat, and this was also palpable at the wrist. On again assuming recumbency the extrasystole continued for a time and then disappeared to reappear on exertion. The rate at the wrist and apex in recumbency was 88. The blood-pressure was 125/80 mm. He stated that his usual systolic pressure was 165. Electrocardiograms showed typical ventricular extrasystoles, apical in character, with slight arborization block.

The abdomen was symmetric, soft and not distended. It contained no free fluid or tumor mass; no muscle spasms or herniæ existed. The liver dulness was normal, and the lower border was smooth and not tender. The spleen was not outlined, and the kidneys were not palpable. The rectum was normal. The neuromuscular system was negative.

The blood examination showed the red cell count to be 5,080,000; the leukocyte count was 12,000. The Wassermann reaction was negative.

The urinary examination showed nothing abnormal.

After six weeks in the hospital the patient showed a slight improvement. The extrasystolic arrhythmia continued, however, for more than six months after he left the hospital. The blood-pressure rose from 125 to 140 (systolic), but the diastolic pressure remained constantly at 80. He stated positively that he never previous to this attack had suffered from extrasystoles. I visited him recently and found him able to attend to office work. He stated that he felt splendidly and that he had had no cardiac embarrassment or pain.

From the history of the onset of his present illness, the severe substernal pain, the fever which lasted about ten days, the great asthenia, the feeble and distant heart sounds, the presystolic gallop rhythm, the extrasystoles occurring for a number of weeks after each normal beat (continuous bigeminy), the low blood-pressure, despite the absence, when first observed, of a pericardial friction rub and the fact that the above-mentioned symptoms came on directly after the onset of a sudden attack of what had been diagnosed as acute indigestion—all these indications led to the diagnosis of a probable thrombosis of a small branch of a coronary artery.

Case XI.—Thrombosis probably of the right coronary artery, followed by a pulmonary infarct and a cerebral embolism, with right-sided hemiparesis and aphasia. Death. (No autopsy.)

The patient, Mr. P. W., aged sixty-six years, was seen by me on November 30, 1920, in consultation with Dr. Russell, of Arlington, Vt.

History. The family history was unimportant. The patient had been a sufferer from asthma for nine years. Three years before he developed a large prostate gland, which caused some difficulty in properly emptying his bladder, otherwise he had enjoyed good health until the onset of the present illness. He denied having had any venereal disease.

The present illness began November 27, 1920, with a pain of a boring squeezing-like character in the region of the cardiac impulse, which immediately passed to the mid-sternum. It continued almost uninterruptedly for three days. He ascribed it to the presence of gas, as he seemed very flatulent and distended. Suddenly at 6.00 A.M., November 30, he had another attack of a most agonizing character, beginning as above described and shooting across the chest to the right arm, into both sides of the neck and to the lower jaw. He was visited immediately by Dr. Russell, who found him very pale, with pinched, ashen-gray features,

bedewed with sweat, anxious facial expression and evidently in great anguish, with fear of impending death ("angor animi"). His radial pulse was rapid, feeble, very irregular and difficult to count. The vessel wall was definitely thickened.

It required ½ gr. of morphin and several doses of glonoin to give him any relief. A few hours later he became very short of breath, cyanosed, had a sharp pain of stabbing-like character in the right chest below the angle of the right scapula, and coughed up some bright pink blood. Dr. Russell found his heart tumultuous and very irregular; the heart sounds distant and feeble, but no friction or endocardial murmur were present. Many fine moist rales at the bases posteriorly were detected.

I saw him at 8.00 P.M. of the same day and found his condition exactly as described by Dr. Russell. No pericardial friction was then heard, but near the angle of the right scapula a definite localized, superficial pleuritic friction rub was discovered and a few subcrepitant rales (pulmonary infarct).

The patient was so shocked and prostrated that the slightest exertion necessary to make the usual physical examination was attended with faintness and marked dyspnea. The blood-pressure was 110/90 mm.

From this history, symptoms and physical signs Dr. Russell had made a probable diagnosis of coronary artery occlusion. In this diagnosis I concurred and believed, because of the evidence of a pulmonary infarct coming so directly after the onset of a severe attack of angina pectoris, that a branch of the right coronary artery was probably the one plugged.

I advised the doctor to watch closely for the onset of a pericardial friction rub. This he did and was rewarded the following day by finding just above the xiphoid cartilage, and over the body of the sternum, a loud pericardial rub, covering an area about the size of a silver dollar.

He continued about the same, with much precordial distress, until December 6, when he was suddenly seized with a temporary loss of consciousness, right facial and lingual paralysis and incomplete motor aphasia and agraphia. I visited him again in the evening of the same day and found him conscious, but drowsy and unable to write or to say only a few words. His tongue deviated to the right and he had a lower right facial paralysis. The grasp of the right hand was also weak. These cerebral symptoms were thought to be due to an embolus dislodged from the left auricle or its appendix. He had from the onset of his illness a continuous temperature, never reaching higher than 101° F.

The patient lived but three weeks, and died of myocardial insufficiency. The pericardial rub lasted but forty-eight hours. No autopsy was permitted.

CASE XII.—Thrombosis of a coronary artery with loud pericardial friction heard over the entire precordium. Recovery.

E. K., aged seventy-seven years, married, was born in Germany.

History. He had always had good health and very moderate in his habits as to tobacco and alcohol. About twelve years before he had had an attack of pain in his chest, which was very severe and similar in character to the present one. He had had several severe attacks since then. He was the manager of a decorative firm, and always did more mental work than physical.

On February 1, at 10.00 A.M., while chopping wood in the basement of his house, he was seized with a severe pain in the chest, which caused him to fall to the floor. I saw him about 10.30 A.M. and found the following conditions: He complained of severe precordial pain and a sensation of pressure which was very severe. The pain extended down the left arm to the wrist. He was very pale; his pulse and heart rhythm were regular. There was a soft, systolic murmur heard at the apex and conducted toward the axilla. The systolic pressure was 160 mm.; the diastolic pressure was 120 mm. The arteries were very much thickened. It was necessary to give morphin to control the pain.

Late the next day there was a doubtful pericardial friction rub, inconstant and heard more distinctly to the right of the apex toward the xiphoid. Twenty-four hours later this rub was much louder and heard over the entire precordium. This intense rub, however, disappeared after a few hours, but could still be heard in the position where first heard. The cardiac rhythm was regular. During the next two or three days there was a slight return of precordial pain.

On February 3 the systolic pressure was 120 mm.; the diastolic pressure was 84 mm. The rhythm was regular. The heart sounds were feeble. The systolic apical murmur was quite indistinct, and the friction rub almost imperceptible. The bowels were very constipated. A mild delirium was present. The temperature had ranged from 90° to 100.5° F. The urine examination showed a specific gravity of 1030, an acid reaction, no albumin, sugar, bile or blood.

February 4 the systolic pressure was 110 mm.; the diastolic pressure was 68 mm. The friction rub was inaudible.

February 6 the systolic pressure was 120 mm. The rhythm was regular, and the heart sounds more distinct. A systolic murmur was distinctly heard.

On March 2 the patient was suddenly seized with a pain in the right side, and respiration became very painful. A very irritable cough developed and he expectorated dark red blood. A friction rub was heard over a small area at the base of the right lung anteriorly. Symptoms disappeared in ten days, only to recur a few days later with physical signs at the base of the right lung posteriorly.

These subjective symptoms and physical signs were thought to be due to a pulmonary infarct. He eventually made a fairly good recovery.

CASE XIII.—Coronary artery thrombosis with recovery.

Mrs. H., aged fifty-eight years, a dressmaker, married, was seen by me on February 24, 1922, in consultation with Dr. Johnson, of Troy, N. Y

History. She had had four living children, no miscarriages and an uneventful menopause at fifty years of age.

On February 21 she was seized with an excruciating substernal pain of a crushing-like nature, accompanied with a sensation of impending dissolution. The pain did not radiate, but continued beneath the body of the sternum, as if the sternum was being crushed in against the spine.

Dr. Johnson gave her $\frac{1}{4}$ gr. of morphin, $\frac{1}{25}$ gr. of glonoin and several doses of codein; but despite this medication, the pain continued through the day and most of the night and then gradually disappeared. She stated that she had had four similar attacks of short duration, otherwise she had enjoyed good health. Physical examination showed a slightly built, somewhat emaciated female, with flushed face and no edema, cyanosis or dyspnea. The radial arteries were decidedly thickened, but easily compressed. The pulse was rapid and regular; the rate was 160. The blood-pressure was 125/100 mm. With a stop-watch a jugular pulsation of 320 per minute was counted, doubtless the auricles were in a state of acute flutter.

The heart sounds were feeble and distant; a slight systolic murmur over the body of the heart was present; a distinct, though faint, to-and-fro pericardial friction sound was plainly audible just above the region of the xiphoid cartilage, as if fast fading away.

Dr. Johnson stated that two days previously the pericardial friction rub was very loud, and that he had followed it as it had gradually faded and disappeared. Fine rales were present at the bases. The chest was hyperresonant throughout. The urine showed a definite trace of albumin and hyalin and granular casts. Its specific gravity was 1022 and the quantity diminished. There was no rise of temperature. A blood count was not done. Digitalis was given in large doses without the slightest effect on the cardiac rate. The tachycardia continued for a period of several weeks, when it gradually diminished. She slowly improved, and in six weeks was able to be up and about, to walk on the level and to do light housework without embarrassment. At present she appears well, although overexertion brings on faintness and substernal pain.

From the symptom of severe angina pectoris, the sudden onset of acute auricular flutter, low systolic blood-pressure, narrow pulse

pressure, acute myocardial insufficiency and a very definite localized pericardial friction rub, there could be but little doubt of the correctness of the diagnosis of thrombosis of a branch of a coronary artery. In view of her great improvement and apparent recovery, it is probable that but a small branch could have been plugged.

Summary. The following is a summary of the salient features of this interesting symptom complex:

1. Sudden severe anginoid pain, substernal or upper abdominal.
2. A pinched ashen-gray or very pale facies, often associated with the sensation of impending dissolution.
3. An acute emphysematous distention of the lungs, with dyspnea or extreme orthopnea and moist crackling rales at the bases of the lung, together with the evidences of the acute onset of cardiac decompensation.
4. An easily compressed rapid thready pulse, which may present almost any form of arrhythmia.
5. A sudden drop in the systolic pressure following the severe pain and early myocardial exhaustion.
6. A cardiac impulse, if palpable, that is a diffuse feeble tap, distant heart sounds and often a tic-tac or gallop rhythm.
7. A localized pericardial friction rub, which is evanescent, appearing as early as a few hours or a day or two after the sudden onset of the agonizing pain. It may be missed if the infarct involves the posterior aspect of the heart.
8. A fever of short duration and of a mild type associated with a polymorphonuclear leukocytosis. This does not occur in simple angina pectoris.
9. Inversion or iso-electric position of the T-wave, with arborization block.
10. Associated with the above described symptoms, the presence of a large tender liver, together with the symptoms and physical signs of pulmonary infarction, is suggestive of thrombosis of the right coronary artery or its branches, while the sudden onset of pulmonary edema or recurring attacks, together with the development of sudden arterial plugging of the vessels of the brain, viscera or extremities, with the characteristic electrocardiogram is highly suggestive of a thrombosis of a branch of the left coronary artery.

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A COMPARATIVE STUDY IN DIGIFOLIN ADMINISTRATION.*

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The first scientific work on digitalis therapy was published by Withering[1] in 1785. Interest in this important contribution to medical science was allowed to lapse until revived by McKenzie during the present generation. Since McKenzie's early work with digitalis numerous investigators have added to our knowledge of the properties, administration and usefulness of this drug. At present digitalis is the most useful drug for the treatment of heart disease.

The early preparations of digitalis were the infusion, tincture and the powdered leaves. It was soon recognized that some cases of acute cardiac decompensation required intensive treatment by other than oral administration. Because of unfavorable properties these early pharmaceutical compounds were unsatisfactory for other than oral therapy. Attempts were made to give the tincture

* I wish to express my appreciation to Dr. F. N. Wilson for his many kind and helpful suggestions during the preparation of this paper.

or infusion by rectum. However, these original preparations caused excessive irritation to the rectal mucosa and it was impossible to have the required amount retained.

One of the first water-soluble preparations suitable for other than oral administration was digalen. According to Wolfer,[2] Naunyn was the first to give this preparation intravenously. This method of administration was further investigated by Naunyn's pupil, Kottmann.[3] This investigator claimed that the reaction was almost instantaneous, and that within a few minutes the maximum effect of the drug was manifested in hearts still retaining reserve power. Kottmann based his claims on: (1) An increase in the strength of the pulse and heart-beat; (2) elevation of the blood-pressure; (3) improvement in the patient's general condition; (4) a diuresis.

Fraenkel[4] introduced intravenous administration of strophanthin for the treatment of heart disease. His original maximum dose was 1 mg., from which several fatalities occurred. The giving of this powerful drug, which occasionally caused death, has fortunately tended to limit promiscuous intravenous digitalis therapy. It has created in many a fear of digitalis administration intravenously and impressed the necessity of carefully considering the therapeutic problem in each case.

There are numerous methods for administering digitalis. Besides the oral and intravenous methods, intramuscular and subcutaneous injections are used and recently rectal insertion has been revived. The present popularity of intravenous therapy is reflected in the variety of digitalis preparations. This condition has been fostered by pharmaceutical houses who enthusiastically exploit the virtues and advantages of their refined preparations. There is little accurate information in support of these claims.

Recently Meyer[5] reported excellent results with rectal administration of dilute tincture of digitalis in certain types of heart disease. In some types of heart failure, other than oral therapy is advantageous to the patient. The giving of digitalis by other than oral administration is, however, rarely necessary or justifiable.

The reasons for administering digitalis by other than the oral method fall mainly into three general groups: (1) The avoidance of irritative gastric symptoms; (2) the unknown factor of absorption from the gastro-intestinal tract; (3) the securing of more prompt and efficient action.

The emetic action of digitalis has been recognized since the time of Withering. Early numerous discrepancies were noted in the deductions from animal experiments and the occurrence of gastric symptoms in patients receiving digitalis therapeutically. It remained for Hatcher and Weiss[6] to demonstrate fully the mechanism of the central emetic action of this drug. They have shown the primary action of digitalis to be on the heart muscle. To produce emesis the nervous connections between the heart and the vomiting center must be intact. This important investigation has

tended to make us lose sight of the fact that there is a direct irritating effect on the gastric mucosa which induces vomiting. The direct action occurs more frequently in patients severely ill or in acute decompensation when the tendency to vomiting is already present. The central emetic action is a delayed and cumulative manifestation of the drug. The direct action occurs after the first dose and shortly after the entrance of the drug into the stomach. Meyer[5] found that emesis was not always due to central stimulation, and he states that by comparison of oral, intravenous and rectal administration he finds that it is not as frequent as supposed.

The principal advantage of modern digitalis preparations is their lessened irritating property. Meyer frequently had patients request digipuratum instead of tincture of digitalis, because it was less irritating to the stomach.

The variability in absorption of different digitalis preparations from the gastro-intestinal tract has frequently been noted. The degree of cardiac decompensation also affects the absorption of drugs. Wolfer[2] found poor absorption after oral administration in cases in which there was congestion of the liver. Meyer[5] likewise noticed lessened absorption from the upper gastro-intestinal tract when hepatic congestion was present while absorption from the lower bowel was undiminished, as he demonstrated by rectal administration. This variation in absorption is due to different venous drainage. The upper gastro-intestinal tract is drained entirely through the liver by the portal system. The rectal venous return is through the hemorrhoidal superior, middle and inferior veins. The superior and medial veins enter the portal system. The inferior vein goes direct to the abdominal vena cava. The draining of part of the blood from the rectum direct to the central collecting system permits drugs readily to reach the heart when liver congestion delays absorption from the upper gastro-intestinal tract. Luthje[7] has also demonstrated this difference in absorption from the upper and lower bowel by the use of glucose in diabetic patients. In two standardized tinctures of digitalis, given by mouth, Wedd[8] found a decided difference in absorption as measured by electrocardiographical changes. Eggleston and Wyckoff,[9] however, after an extensive study of this question, concluded that the factor of absorption is of sufficient uniformity with good galenical preparations to permit the establishment of an average total therapeutic requirement. This conclusion is confirmed in the work of Pardee[10] and Robinson.[11] The amount necessary by oral administration for complete digitalization on the basis of body weight apparently may be fairly accurately determined. The rapidity of absorption must, however, depend on the degree of cardiac decompensation and congestion.

We have tried to determine more accurately the variation in rapidity and efficiency of action of the same digitalis preparation given by different methods. The rapid and efficient action of

strophanthin intravenously is sufficiently well known to require no comment. The poor action of strophanthin given by mouth is due to its poor absorption from the gastro-intestinal tract. Cohn and Levy[12] have compared the action of digipuratum by mouth and strophanthin intravenously in patients with auricular fibrillation. The two drugs were given in divided doses, and in most cases the periods of administration were the same. By electrocardiographical changes they noted that the effect of strophanthin intravenously in divided doses may not be noted for two hours. Digipuratum by mouth in divided doses may cause changes in a little more than two hours. The strophanthin action rarely lasted more than five days while digipuratum effects lasted usually ten days and as long as twenty-three days. Strophanthin caused but slight and transient changes in the T-wave of the electrocardiogram, while digipuratum caused striking and prolonged effects. Morris[13] gave dilute tincture and infusion of digitalis intravenously and obtained immediate action with no harmful secondary results. He has failed to give records of his experiments, so his work is not suitable for comparison. Fulton[14] found definite reduction in the heart-rate six to eight hours after intravenous administration of strophanthin, but does not state dosage or time intervals. Pratt[15] noted striking benefit with intravenous amorphous strophanthin in cases of heart failure with regular cardiac rhythm, when the patients had failed to respond to digitalis by mouth. This observation is unusual in view of the accepted belief of the mutually interchangeable action of the various bodies.

Methods of Investigation. Patients with auricular fibrillation comprise about two-thirds of our cases. The recorded results are from 25 patients, 10 of whom could not be used in their entirety because of death, defective records or some other mishap. The hearts were in varying stages of decompensation, and no effort was made at selection. All patients were confined strictly to bed and maintained on the usual low protein, low caloric diet throughout the entire period. Patients with edema were limited to 1500 cc of fluid daily. Morphin was used as a sedative, but no other medication was permitted. The ampoule form of digifolin was used in all cases. After some preliminary work the dose chosen was 5 ampules (0.5 gm. of standardized digitalis leaf), given twice daily. The interval between doses was in most cases twelve hours, as Pardee has shown that the maximum effect is obtained in about six hours, and that intervals of twelve to eighteen hours are best in order to allow early toxic signs to manifest themselves. Two electrocardiograms were taken daily, usually about six hours after administration. All electrocardiograms, including the control curve, were taken with the patients in bed.

Effect on Heart-rate. One of the most characteristic effects of digitalis on auricular fibrillation is slowing of the rate. As digifolin (5 ampoules) was given twice daily, the apex-rate was counted every

five, or in a few cases, every ten minutes thereafter for two hours, then every half hour for four hours and every hour for the following six hours.

The accuracy of the counts was carefully supervised. In patients with auricular fibrillation a preliminary sudden fall in heart-rate was noted within the first twenty minutes following the intravenous injection of the drug. This fall in heart-rate was not of sufficient degree or frequency to allow us to draw any definite conclusions. The results are given in Table I. The period of maximum slowing was considered as that point on the chart at which the apex count showed the greatest decrease in rate below that at the time of administration. A decrease of less than 10 beats has not been considered significant.

TABLE I.—EFFECT OF DIGITALIS ON THE HEART-RATE WHEN ADMINISTERED BY DIFFERENT METHODS.

Method.	Intravenous.	Intramuscular.	Mouth.
Earliest noted maximum slowing	1 hr.	1 hr. 30 min.	2 hrs. 45 min.
Average time that maximum slowing was noted	3 hrs. 50 min.	4 hrs.	6 hrs.
Latest noted maximum slowing	6 hrs.	6 hrs. 15 min.	11 hrs. 30 min.

The intravenous findings were obtained from 23 single administrations. The maximum slowing was noted within one hour or as late as six hours, but occurred on an average in three to four hours. In 28 intramuscular injections the maximum slowing was noted in one and a half hours or as late as six and a quarter hours, but it occurred at an average of four hours. The average time intervals required for obtaining maximum slowing of the heart-rate by divided doses of digifolin given intravenously or intramuscularly are approximately the same, intramuscular injection taking but a slightly longer time.

In oral administration the earliest maximum slowing occurred in two and three-quarters hours, the latest in eleven and a half hours and the average at about six hours. The average time period for maximum slowing of the heart-rate in oral administration compares favorably with that found by Pardee.[10] In giving massive doses of digitalis by mouth Robinson[11] found the period for maximum slowing of the ventricular rate to be from two to five hours. It appears to take two or three hours longer to obtain maximum slowing of the heart-rate in auricular fibrillation by oral than by intravenous or intramuscular injection of digifolin when the drug is given under fixed conditions.

Comparative Efficiency as Measured by Digifolin Requirement. That we might compare the amount of digifolin causing the earliest changes and the full therapeutic effect on the heart in the three methods of administration, electrocardiograms were taken twice daily. The curve in most cases was taken about six hours after medication; in a few intervals of twelve hours elapsed. The early action of the drug on the heart was noted by changes in the T-wave.

This has been shown by Cohn, Frazer and Jamieson[16] to be the earliest manifestation of digitalis action. They considered lowering or inversion of the T-wave, or an isolectric T-wave, evidence of activity. They found that this change occurred in most cases before any gastro-intestinal symptoms were noted. Wedd[8] found the earliest electrocardiographical change to be in the T-wave. Pardee[10] found T-wave changes in from two to four hours after the oral administration of tincture of digitalis equal to 1 minim of tincture per pound of body weight. The maximum effect occurred in from six to seven hours.

The data were obtained from 15 unselected cases and are given in Table II. Many of these patients had auricular fibrillation, and a brief history of each is given. The following patients received digifolin intravenously:

Report of Cases. CASE I.—Miss I. R., aged forty years, had had frequent attacks of tonsillitis. Her first symptoms of cardiac weakness had occurred one and a half years previously. The heart was slightly enlarged. There was stenosis of the mitral valve, and auricular fibrillation was present. She was dyspneic and complained of palpitation. An associated toxic goiter complicated her illness.

CASE II.—Mr. C. L., aged fifty-five years, had an advanced arteriosclerosis, definite cardiac enlargement, auricular fibrillation and cirrhosis of the liver. He was dyspneic and had cyanosis, with edema of the feet and legs, and complained of palpitation and orthopnea.

CASE III.—Mr. D. H., aged forty-nine years, had had cardiac symptoms during the preceding year. He had advanced arteriosclerosis, cardiac enlargement and auricular fibrillation. He had cyanosis, was dyspneic and complained of gastric disturbances. There was a large collection of ascitic fluid and edema of both legs.

CASE IV.—Mrs. C. C., aged forty-five years, had had an attack of "rheumatic fever" at the age of fourteen years associated with symptoms of cardiac decompensation. A second attack of rheumatic fever occurred at the age of thirty-five years. She had mitral stenosis, enormous cardiac enlargement, auricular fibrillation, dyspnea, palpitation and edema.

CASE V.—Mr. E. F., aged forty-eight years, had had rheumatic fever at the age of twenty-three years and again at forty-four years. He had had frequent attacks of tonsillitis. His symptoms had appeared one year previously. He showed a moderate degree of arteriosclerosis, mitral stenosis, auricular fibrillation, moderate enlargement of the heart, cyanosis and dyspnea. He complained of palpitation.

The following patients received digifolin by mouth:

CASE VI.—The history of Miss I. R. is given under those who received intravenous therapy. Sufficient time elapsed between her two periods of digitalization to avoid any question of persistent digitalis action.

TABLE II. COMPARATIVE EFFICIENCY OF THE THREE METHODS OF ADMINISTRATION AS MEASURED BY DIGIFOLIN REQUIREMENT.

Patient.	Case No.	Method.	Weight, kg.	Amount digifolin at first E. K. G. change.	Cat unit per kg.	Digifolin for full therapeutic effect.	Cat unit per kg.	Reason drug was discontinued.	Change in patient's condition.
Miss I. R.	1	Intravenous	54.5	5	0.0600	20	0.2414	Slow apex-rate; nausea	Improved.
Mr. C. L.	2	Intravenous	70.4	5	0.0470	28	0.2640	Nausea-anorexia; slow apex-rate	Much improved.
Mr. D. H.	3	Intravenous	61.8	10	0.1064	20	0.2128	Bigeminal pulse	Much improved.
Mrs. C. C.	4	Intravenous	67.0	5	0.0490	25	0.2450	Slow apex-rate (52)	Improved.
Mr. E. F.	5	Intravenous	67.0	5	0.0490	20	0.2000	Slow rate; long pauses	Improved.
Average	..	....	...	...	0.0623	...	0.2326		
Miss I. R.	6	Mouth	53.6	10	0.1220	35	0.4350	Nausea; anorexia	Improved.
Miss L. B.	7	Mouth	39.0	10	0.1690	20	0.3380	Nausea; vomiting	Slight improvement.
Mrs. L. H.	8	Mouth	99.0	10	0.0664	20	0.1328	Slow apex-rate (42)	No change.
Mr. D. N.	9	Mouth	72.7	15	0.1370	45	0.4120	Rapid irregular pulse	Slightly improved.
Mr. W. L.	10	Mouth	68.0	10	0.0969	43	0.4150	Nausea; vomiting; prolonged pulse-rate	Improved.
Average	..	....	...	...	0.1182	...	0.3465		
Mr. W. N.	11	Intramuscular	78.1	5	0.0420	20	0.2520	Nausea; vomiting	Much improved.
Mr. I. W.	12	Intramuscular	77.0	10	0.0850	30	0.2550	Nausea; vomiting	Improved.
Mrs. M. K.	13	Intramuscular	84.0	5	0.0390	30	0.2346	Nausea; vomiting	Slightly improved.
Mr. A. F.	14	Intramuscular	91.0	10	0.0720	28	0.2030	Slow apex-rate; nausea	Improved.
Mr. C. H.	15	Intramuscular	93.0	10	0.0700	43	0.3080	Slow apex-rate; nausea	Much improved.
Average	..	....	...	...	0.0610	...	0.2505		

CASE VII.—Mrs. L. B., aged sixty-one years, had a history of rheumatic fever. The heart was slightly enlarged. Mitral stenosis was present with hypertension. An orthodiagram showed a wide dense aortic shadow; the Wassermann test of the blood was 4+. Slight signs of cardiac failure were present.

CASE VIII.—Mrs. L. H., aged fifty-nine years, was first admitted in 1918 for cardiac failure with auricular fibrillation. At the second admission, in October, 1922, she had a few cardiac symptoms. She showed slight arteriosclerosis, auricular fibrillation, moderate cardiac enlargement and no valvular lesions. There was a history of rheumatic fever at the age of sixteen years.

CASE IX.—Mr. D. N., aged sixty-four years, had an essentially negative past history. He had noticed slight dyspnea and palpitation on exertion for ten years. The acute condition had been present for nine weeks, with increasing dyspnea and palpitation. There was a large amount of edema in both legs. He showed advanced arteriosclerosis with moderate cardiac enlargement.

CASE X.—Mr. W. L., aged thirty-eight years, gave an indefinite history of rheumatic fever. He complained of dyspnea, palpitation and pain over the precordium and in the left side of his chest. A high grade of cyanosis and edema were present, with mitral stenosis, enormous cardiac enlargement, pulmonary congestion and clubbed fingers.

Digifolin was given by intramuscular injection in the following cases:

CASE XI.—Mr. W. N., aged fifty-three years, had a history of frequent ulcerative sore throats and syphilis. His Wassermann test was 4+. He showed an advanced arteriosclerosis, mitral stenosis, enormous cardiac enlargement, auricular fibrillation and aortitis. Intense cyanosis was present, also dyspnea and orthopnea with an extreme edema of his legs and swelling of the abdomen.

CASE XII.—Mr. I. W., aged sixty years, whose past history was essentially negative, had extreme swelling of the arms and legs with marked dyspnea and palpitation, advanced arteriosclerosis and enormous cardiac enlargement. The orthodiagram showed a dense aortic shadow. He had acute decompensation.

CASE XIII.—Mrs. M. K., aged thirty-five years, had had one attack of rheumatism and a severe puerperal infection six years previously. She also had a history of syphilis. The heart was enlarged, the neck veins engorged and aortitis with aortic regurgitation were present. There was stenosis of the mitral valve. Dyspnea and palpitation with slight edema of the legs were present.

CASE XIV.—Mr. A. F., aged fifty-seven years, had an essentially negative past history. He had extreme arteriosclerosis, cardiac enlargement, cirrhosis of the liver and auricular fibrillation. The left arm and leg were paralyzed as a result of a preceding "stroke."

He was dyspneic and had cyanosis with extreme edema of the lower half of his body. Palpitation was complained of, and severe mental deterioration was present.

CASE XV.—Mr. C. H., aged fifty-seven years, whose father and several brothers had died of "heart disease," had an advanced arteriosclerosis, cardiac and hepatic enlargement, engorged neck veins, auricular fibrillation, dyspnea, cyanosis and edema. The chief complaint was palpitation.

There was a wide variation in the patients' weight, with considerable difference in the amount of digifolin required to produce the earliest and maximum effects. Comparison has been made on the cat unit per kilogram basis.

For standardization of our digifolin we used the rapid digitalis-ouabain method of biological assay developed by Hatcher and Brody.[17] Five cats were used, and 1.52 cc of the lot of digifolin used was found to equal 1 cat unit.

Considerable variation was found in the cat unit per kilogram required to initiate the first electrocardiographical changes. The average amount of digifolin required to induce the alteration in the T-wave was 0.0623 cat unit per 1 kg., by intravenous injection, 0.061 cat unit per 1 kg., by intramuscular injection, and 0.1182 cat unit per 1 kg., by oral administration. Intravenous and intramuscular injection are of equal efficiency in the amount of digifolin thereby required to produce early effect. By oral administration the drug appears about half as efficient.

The maximum activity was based on both clinical and electrocardiographical changes. In some the appearance of anorexia, nausea or vomiting were our indications of complete digitalization, while others were measured by a heart-rate below 60, bigeminal pulse or exaggerated electrocardiographic changes. A decided uniformity was noted in the patients who received digifolin intravenously. Among those receiving digifolin by mouth, the low figure of 0.1328 is noted for Case VIII. By intramuscular therapy an amount (0.308) considerably higher than the average was obtained for Case XV. These wide variations from the average were unusual, and we can offer no explanation for them. In intravenous and intramuscular injections the amount of digifolin necessary to produce the earliest noticeable effects and the full therapeutic effect is apparently almost the same. When the drug is administered by mouth it appears that it is about half as efficient in relation to the amount required to produce these same effects.

Comparative Efficiency as Noted by Time of Action. The question of the degree of efficiency, as denoted by the amount of digifolin per kilogram required for the three methods of administration has been stated. It remained to compare the three methods in relation to the average time required to produce earliest and maximum effects. Digifolin having been given twice daily at intervals of

twelve hours, two electrocardiograms were taken, in most cases, six hours following each administration of the drug. The period for the earliest effect is a measure of the time elapsing from the giving of the first dose of digifolin until the first change is noted in the T-wave of the electrocardiogram. The maximum time period is a measure of the time elapsing from the initial dose to the appearance of toxic symptoms as noted either clinically or electrocardiographically. The average cat unit per kilogram of body weight for the two periods has been taken from Table II.

We have not attempted to determine the actual time of the earliest and maximum effects on the heart, but rather to compare these changes as noted under fixed conditions for the three methods of administration.

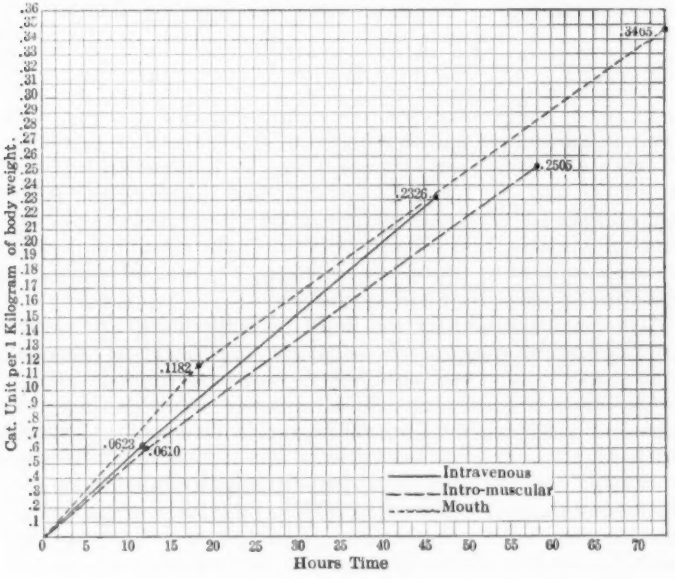

FIG. 1

The results in Fig. 1 demonstrate the superior comparative efficiency of intravenous digitalis therapy, both in rapidity of action and quantity of drug required. By this method activity was first noted at an average of ten and a half hours with digifolin equal to 0.0623 cat unit per 1 kg. of body weight. An average maximum activity occurred in forty-six hours with digifolin equaling 0.2326 cat unit per 1 kg. of body weight. Early effects by intramuscular injection were noted with 0.061 cat unit per 1 kg. of body weight, which is similar to the intravenous requirement. However, there was a slight delay in time, which had been previously noted in the slightly longer delay in slowing the pulse (Table I). This slight

delay, presumably due to slightly slower utilization, is apparently accentuated by succeeding doses, as the maximum effect is noted in about one-third longer time. The relative efficiency of intravenous and oral administration in the amount of drug per unit of body weight required has been previously discussed. In comparing the time intervals, we note that intravenous is almost twice as efficient an oral administration in producing early electrocardiographical changes. This same proportion holds approximately true in the production of the full therapeutic effect.

Unfavorable Results from Intravenous Administration of Digifolin. In Wolfer's paper, published in 1921, he states that he had never observed, and had been unable to find in the literature, the occurrence of unfavorable symptoms or death from digitalis given intravenously.

It was our unfortunate experience to observe 2 cases in our brief series in which the patients' deaths may possibly have been in part due to the administration of digifolin intravenously. A brief summary of each case is presented:

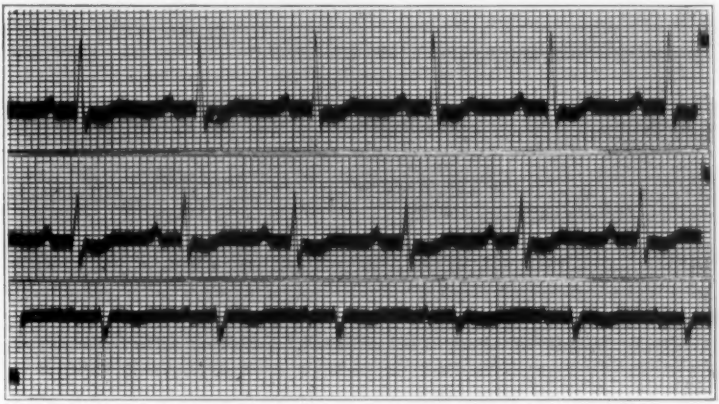

FIG. 2.—Miss A. M.: Leads I, II and III taken at admission. This showed only inversion of the T-waves in all three leads.

CASE XVI.—Miss A. M., aged fifty-three years, entered the University Hospital in a state of extreme cardiac decompensation. Her symptoms of dyspnea, palpitation, weakness and swelling of the legs and abdomen had been slowly but gradually increasing since an attack of rheumatic fever ten years previously. These symptoms had become acute during the last two months. She had spells, increasing in frequency and severity, of acute orthopnea, palpitation, a sense of suffocation in her chest and nausea with vomiting. At the time of admission there was extreme cyanosis. Examination revealed mitral stenosis, aortic regurgitation, enormous edema of both legs, with fluid in the chest and abdominal

cavities. She received 5 ampoules of digifolin intravenously at once and 20 ampules in all over a period of forty-eight hours. An early digitalis effect was noted in the curve. One hour following the last administration the patient's condition appeared much improved, but the curve showed a complete auriculoventricular dissociation with variations in the position of the ventricular pacemaker. Another curve taken two hours later showed the same condition with numerous extrasystoles. Four hours after receiving the last dose of digifolin her pulse suddenly fell, and without warning respiration ceased.

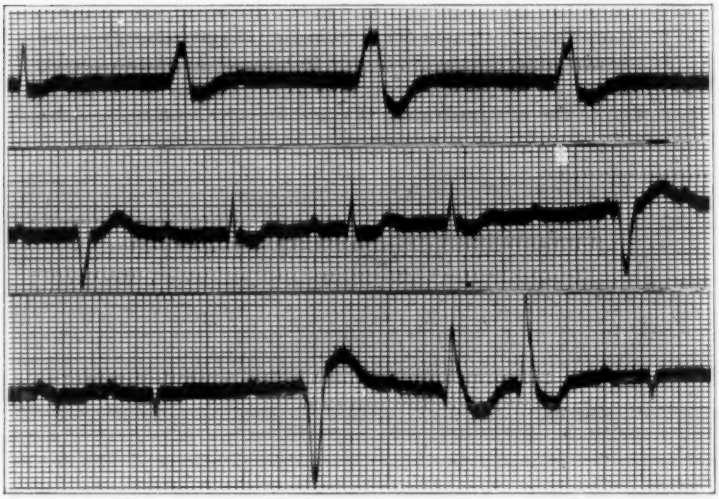

FIG. 2.—Miss A. M.: Leads I, II and III taken three hours before death, showing complete auriculoventricular dissociation, with variations in the position of the ventricular pacemaker.

CASE XVII.—Mr. W. W., aged seventy-one years, complained of dyspnea, orthopnea, weakness and insomnia. The cardiac condition had been present four years, becoming acute during the last six weeks. At entrance he had Cheyne-Stokes respirations, an enormously enlarged heart, but no murmurs. There were many extrasystoles, and the heart sounds were distant. The aortic second sound was much accentuated and well heard to the left of the sternum. The electrocardiogram showed a right bundle branch-block. The patient was given digifolin intravenously, 20 ampoules in all, in 5-ampoule doses twice daily. Following the last injection he appeared improved until suddenly, while conversing with his relatives, he fell backward gasping, extremely cyanosed, and the heart stopped beating. For several seconds after the heart sounds

had become inaudible a rapid fluttering movement was noticed in the external jugular vein on the right. An electrocardiogram taken on the day preceding death showed the same cardiac disturbance

FIG. 3.—Mr. W. W.: Leads I, II and III taken shortly after admission, showing a right bundle-branch block.

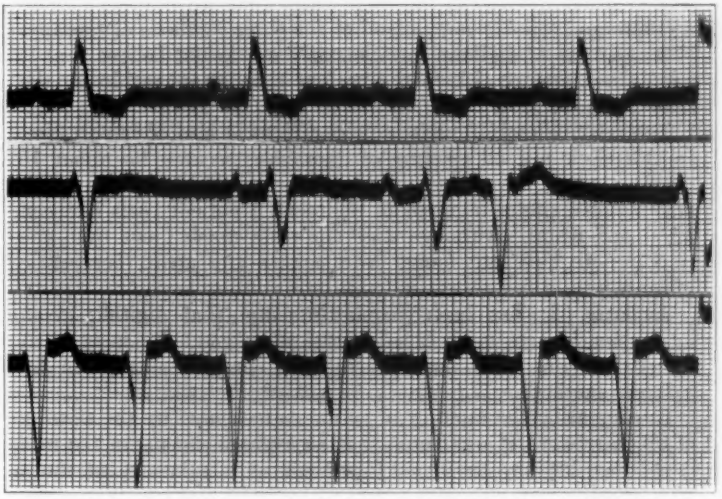

FIG. 4.—Mr. W. W.: Leads I, II and III taken six hours before death, showing right bundle-branch block with numerous extrasystoles. The *P–R* interval was prolonged (0.24), and the third lead showed idioventricular beats at a rate of about 100.

as at entrance. The curve taken six hours before death showed right bundle branch-block with numerous extrasystoles, a prolonged *P–R* interval (0.24), and in the third lead idioventricular beats at a rate of about 100.

The occurrence of these 2 cases in our small series of patients impressed on us the possibility of unfavorable results from too intensive treatment. We were unable to secure necropsy in either case, but the late changes in the electrocardiograms, together with the type of death in both cases, made us feel that the digifolin may have been a contributing factor.

There was extreme decompensation in both cases, and clinical and electrocardiographical evidence showed signs of advanced cardiac degeneration. The factors in these cases which caused death while other patients in like circumstances and under the same treatment improved are impossible to state.

We chose digifolin for use in this investigation because we found it a favorable preparation for use in the three methods of administration. We did not believe that it had any special therapeutic advantages. In most instances a good tincture of digitalis is preferable to other preparations.

The indiscriminate use of digitalis preparations by intravenous or intramuscular methods is not advocated. There are cases in which the severity of the symptoms demands immediate and intensive treatment. It was for these cases that we desired a more accurate and reliable comparison of the three methods of therapy. From our use of digifolin intravenously we do not believe that it carries any greater risk to the patient than strophanthin by the same method.

The relative cost of various preparations is also of importance. In this clinic a good tincture of digitalis is secured for about 15 cents an ounce. An ounce of digifolin costs $3.90. The average amount of digifolin required to digitalize a patient costs between $2.50 and $4.00. Although digifolin costs much more than the tincture, we have not found it to possess any great therapeutic advantage.

Summary. It has been frequently noted that digitalis given intravenously acts more rapidly than when given by mouth. A comparison has been made of different preparations given by different methods.

In comparing the rapidity of action as measured by the slowing of the heart-rate, it was noted that an average slowing of the rate is obtained between three and four hours by intravenous, at about four hours by intramuscular and at six hours by oral administration.

The amount of digifolin required to show the earliest and full therapeutic effects is about equal for intravenous and intramuscular injection. By oral administration it required about half again as much of the drug.

The average time required for digifolin to show the earliest and maximum effects with the three methods of administration has been obtained. The comparison of these time intervals closely approximates the comparison of the digifolin requirements.

The possible unfavorable result of intensive therapy has been mentioned.

The use of digitalis by other than the oral method of administration has not been advocated.

The cost of different preparations of digitalis has been mentioned as an important factor in treatment.

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THE EFFECT ON THE BLOOD OF IRRADIATION, ESPECIALLY SHORT WAVE LENGTH ROENTGEN-RAY THERAPY.*

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Introduction. The physiological effects of exposure to roentgen-rays and radium are assuming increasing importance in clinical medicine; particularly with the advent of the use of apparatus of

* Drs. G. W. Holmes, L. B. Morrison, M. C. Sossman and R. G. Giles administered the treatments. It is a pleasure to acknowledge our indebtedness to them for their helpful suggestions. The coöperation given by the staff is duly appreciated, especially that of the director, Dr. Robert B. Greenough. The careful technical assistance given by Miss Geneva Daland and Miss Margaret Weld is also acknowledge with gratitude. This paper is No. 32 of a series of studies in Metabolism from the Harvard Medical School and allied hospitals. The expense of this investigation has been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

high voltage delivering short wave lengths. It has long been recognized that desirable therapeutic irradiation produced slight blood alterations, and that excessive irradiation produced profound changes in the hematopoietic system. There has been a general impression that a profound effect on the blood, which might lead to disastrous results, would become prevalent with the administration of the new short wave length therapy. With the installment at the Collis P. Huntington Hospital of Harvard University of a high voltage apparatus designed by Prof. William Duane, a study of the effect of its rays of short wave length on the formed elements of the blood has been undertaken with a view to determining whether a biological reaction occurred that would be of value in indicating the safe use of the apparatus.

Résumé of the Literature. In order to evaluate the known effect of irradiation on the blood, a brief review of the literature is given below. For the benefit of those who wish to study the subject in detail, an essentially complete bibliography is appended. (Articles starred are considered to be the most serviceable.)

The data in the literature on the effects of irradiation on the blood are confusing, owing chiefly to the utilization of many different kinds of apparatus delivering different degrees and qualities of light. Details regarding the amounts of irradiation utilized have often been omitted, hence only generalized statements are made below concerning the blood changes after irradiation with either roentgen-rays or radium.

It has become generally accepted that biological reactions after exposures to roentgen-rays and radium are essentially the same, the degree of reaction depending upon the quantity of irradiation taken into the organism. The location of the exposure appears not to create a fundamental difference in the alterations that occur in the blood. Levin[32] states, however, that radium causes less general disturbance to the blood and hemopoietic system than does corresponding doses of roentgen-rays. It is also his belief, from animal experimentation, that the effect of irradiation on the blood is dependent upon the square surface of entry of irradiation into the organism to a far greater extent than upon the size of the dosage administered.

Heineke,[22a] in 1904, made the first careful histological studies of the blood and blood-forming organs following roentgen-ray exposures. His experiments were made upon small animals. He demonstrated that the lymphoid tissue of the body was primarily affected, and that there developed a degeneration of lymphoid follicles in the spleen and lymph glands, and a diminution in the number of lymphocytes in the circulating blood. He also found that there was a marked diminution in the number of white cells after heavy irradiation, beginning after the second day, with a predomination of polymorphonuclear neutrophiles. After several days the lympho-

cytes almost entirely disappeared, while the absolute number of polymorphonuclear and large mononuclear forms showed scarcely any change. From his studies on the bone-marrow he found that the white cells, with few exceptions, were destroyed. This destruction of white bone-marrow cells was apparent in three hours after exposure, and reached its height after eleven hours. The destructive process terminated after five or six days. Heineke noted that the injured bone-marrow was capable of regeneration, which commenced before the destructive action ceased and was completed by the end of the third or fourth week. He suggested that the diminution in the circulating lymphocytes is referable directly to the selective destruction of the lymphogenic tissue by roentgen-rays. These observations on the hemopoietic system have been confirmed by Warthin,[68] Aubertin and Beaujard, [4a, 4b] and others. [30, 38a] It has also been shown [3, 12, 29, 53, 67] that if the irradiation is sufficient, actual complete aplasia of the marrow occurs with its characteristic peripheral blood picture.

During the next few years, following this pioneer work of Heineke, reports of intensive studies of the circulating blood after irradiation appeared in the literature. Practically all the recorded observations were made on small animals with only an occasional observation on patients. Aubertin and Beaujard[4b] were apparently the first to report that prior to leukopenia there developed a primary transient leukocytosis. They found that the leukocytosis was due almost entirely to an increase in the polymorphonuclear neutrophiles. Since their report many [4a, 10, 17, 49, 63, 65] have observed that an initial leukocytosis occurs in both animals and man after any amount of irradiation in contrast to the leukopenia which develops only after relatively large doses. The height of this leukocytosis apparently varies in animals and man; in animals an increase of 100 per cent in the number of circulating leukocytes is common, while in man the increase seldom amounts to over 50 per cent. The leukocytosis usually starts about two hours after roentgen-ray treatment, and has reached its height in twelve hours. It persists, on the average, for not longer than twenty-four hours. The height of the leukocytosis does not seem to be dependent upon the character of the irradiation. When radium is used the leukocytosis lasts longer than when roentgen-rays are used; often forty-eight hours. This longer duration may be due to the fact that radium is often applied for a much longer period of time than the roentgen-rays.

All observers [21, 33, 35, 38, 57, 61, 69, 70] have found that following the leukocytosis there often occurs a marked decrease in the number of white blood cells, especially the lymphocytes. This decrease amounts to an actual leukopenia if sufficient irradiation is used. In experimental animals the white cells have often been recorded as low as 1000 per cu.mm., requiring five to fifteen days before they returned to normal numbers. This degree of reduction of

the white cells rarely has been observed in man following customary therapeutic doses of irradiation, though excessive irradiation may lead to such a reduction. In the early literature, counts of 4000 white cells per cu.mm. are occasionally recorded in man, but such counts were only transient and the normal level was reached in a few days. This contrast between the effects of the rays on animals and man is but one of degree and can be accounted for by the proportional difference in the size of the doses used. However, since the more recent clinical reports of the effect on the blood of large doses of radium and roentgen-rays, leukopenia of greater degree and of longer duration than formerly recorded, is being observed following treatment. Leukopenia, following intensive treatment, has been recorded as persisting from three to five weeks, and Heim[21] states that it may be even eight to twelve weeks before the white cells return to normal. The advent of the high voltage machine delivering rays of short wave length is not wholly responsible for the recent increase in the frequency of leukopenia. This is because larger doses of irradiation have been employed with all forms of apparatus during the last three to four years. The blood changes now being observed following intensive irradiation are quite comparable to those observed in small animals many years ago, because the large doses now being used therapeutically approach quantitatively the doses originally employed in animal experimentation. It is noteworthy that information in the literature is scant concerning the ease with which leukopenia is produced by second courses of treatment.

To prove whether the leukopenia produced by irradiation is due to a direct effect on the circulating blood or to a suppression of activity of the bone-marrow, Benjamin *et. al.*,[7] performed some ingenious experiments. They showed that it is possible to produce the characteristic changes in the circulating blood (leukocytosis followed by leukopenia) not only by irradiation of the blood-forming organs, but also by irradiation of the isolated blood. A cardinal difference in the effect of irradiation of the two tissues is that regeneration occurs with astonishing ease in the latter instance, while after the bone-marrow is exposed seven to ten days are required for regeneration. They conclude that the transient changes occurring in the blood during the first twenty-four hours are accompanied by a destruction of leukocytes in the blood stream while the more prolonged alterations are due to injury of the hemopoietic system.

It has been well established that the lymphocytes are the most sensitive of all the blood cells to irradiation. Since Heineke[22a] demonstrated in animals a diminution of the number of circulating lymphocytes and a destruction of lymphoid tissue following exposure to roentgen-rays, this phenomenon has been investigated by many,[5, 7, 16, 36, 38, 56, 59] especially Mottram[39, 41] and Murphy.[44, 45, 47] The

results show clearly that while relatively large doses of irradiation cause a marked decrease in the number of circulating lymphocytes, distinctly small doses act as a stimulus to the lymphogenic organs and cause a lymphocytosis. The degree of lymphopenia is not necessarily proportional to the degree of leukopenia. Quite comparable to the effect of small doses of roentgen-ray or radium irradiation is the effect of the similar light rays from the sun, as it has been shown by Aschenheim,[1] Clark,[14] and others, that there occurs a relative and actual increase in the number of circulating lymphocytes after exposure to direct sunlight.

The percentage of polymorphonuclear neutrophiles varies in inverse proportion to the percentage of lymphocytes at all times following irradiation. The absolute numbers of polymorphonuclears are increased, except with leukopenia, when they may become reduced to 50 per cent of their original number; however, their percentage still remains high.

Coincident with the drop in the lymphocytes, the polymorphonuclear eosinophiles undergo a decrease. None may be observed when leukopenia develops. Later they increase over a period of days to weeks, reaching often above normal and sometimes as high as 15 per cent, then returning to normal in a similar period of time. Aubertin and Beaujard[4a] found in animals on the fourth day following exposure an increase of eosinophiles that persisted for two to three weeks. Later observations on man by Heim,[21] Masieri,[35] Schroeder,[61] and Koenigsfeld,[27] indicate that eosinophilia is a late rather than an early manifestation of the effect of irradiation, the primary rise occurring some weeks after exposure. Petersen and Saelhof[50a] found eosinophilia (5 to 20 per cent) developed for a number of days following irradiation over the livers of dogs. They did not observe such an increase in eosinophiles after exposures of other organs.

No constant changes in the character or number of polymorphonuclear basophiles have been observed following irradiation.

After irradiation little or no change in the numbers or character of the large mononuclear cells has been discovered by most observers. Wetterer, Band and Nemnick[70] are the only ones to report that many of these cells appear in the blood stream after irradiation.

Various observers (Aubertin and Beaujard[4a] and others[5, 24, 38]) have noted following irradiation of animals two types of histological changes in the white cells of the peripheral blood; one to be interpreted as due to destruction and premature death, and the other indicative of youth. Leukocytes showing evidence of histolysis of the nucleus and cytoplasm with abnormal granulations have been frequently recorded in animals in the first week after exposure. During this period of time fragmented white cells were observed often, and sometimes in abundance. These changes occurred especially in the polymorphonuclear cells, but "mononuclear cells"

(Morris[38] includes lymphocytes) also exhibited such alterations. Coincident with the many degenerating cells there appeared in the blood stream an increased number of immature ones. These consisted for the most part of young polymorphonuclear neutrophiles although an occasional myelocyte was observed. The occurrence of degenerating and immature cells in man after irradiation has been referred to but little.

There are relatively few observations recorded on the effect of irradiation on the blood platelets. Helber and Linser[24] and Duke[19] found that there was a decided decrease in the number of circulating blood platelets in small animals following heavy irradiation, while smaller doses apparently stimulated their production and caused a rise. Similar observations of the effect of radium are recorded by Mottram.[39e] Bucky and Guggenheimer[9a] among others have observed over 100 per cent increase in the number of blood platelets in man following erythema doses of roentgen-rays.

The effect of irradiation on the red cells and hemoglobin is not so clearly defined in the literature as the effect on the white blood cells. It is evident that important changes do not occur after customary therapeutic irradiation unless repeated many times. Some have reported that if considerable anemia exists then the red cells are adversely affected. Heineke,[22a] in his earliest observations, found no change in the number or form of the red cells or the amount of hemoglobin during the first twelve days after exposure to the roentgen-rays. During the third week he found that there was a slight decrease in both of these elements. His later observations in the clinic failed to support this view, however, as he found a decided increase in the red cells and hemoglobin in patients after roentgenotherapy. It is evident from reports that fluctuations in the hemoglobin and red cells occur after irradiation, but confusion arises owing to a lack of a distinction between the effects of irradiation and changes in the blood due to improvement of the patient. The current opinion seems to be fairly evenly divided between those [8, 9a, b, 15, 21, 22a, b, 61] who believe that there is an increase and those [3, 10, 20, 25, 39b, 55, 62] who recognize a decrease in the number of red cells and the percentage of hemoglobin, and those [6, 36, 38, 60] who believe there is no appreciable change in these two elements after irradiation. It seems probable that this difference of opinion may be due to variation in the size of the dose of irradiation used, as well as variations in the health of different patients. It is well known that prolonged and excessive exposure to irradiation may lead to anemia[29, 53] an ill-effect that never has been observed after a single exposure. Nucleated red corpuscles have been noted in the circulating blood of animals, but not in man when the bone marrow was essentially normal, following large doses of irradiation. No distinct or constant alterations in the size, shape, or staining qualities of the red blood corpuscles

have been observed in man or animals following therapeutic irradiation.

The blood picture of those people chronically exposed to irradiation, as roentgen-ray and radium workers, is extremely variable and does not directly concern us here. Suffice it to say, that the blood picture may be one that indicates varying degrees of marrow insufficiency, while occasionally, if the exposure is sufficient, actual aplasia may develop.

Cases Studied and Methods. From the above résumé of the literature, it is evident that there is ample information indicating that sufficient irradiation of any part of the body leads to lymphopenia and leukopenia. In spite of the lack of comprehensive data in the literature, it would appear that the degree and duration of the lymphopenia and leukopenia are more marked and longer with a larger than a smaller dose; that though the degree may be the same with different doses, the duration will be longer with the larger dose. The effect of the amount of surface area irradiated has been shown to play an important part in alteration of the blood in animals, but in man little attention has been given to this factor. Investigations reported below were undertaken with a view to determine the degree and duration of changes in the white cell count produced by desirable therapeutic doses of short wave length roentgen-rays as contrasted with roentgen-rays of longer wave length in patients not suffering from any fundamental disorder of the hemopoietic system. In addition to the white cell count, observations on all the formed elements of the blood were made to determine what changes occurred and to learn how further to evaluate alterations of the blood in regard to safe and efficient treatment.

The data presented were obtained on 42 patients with various forms of malignant disease.* These cases have been divided into three groups dependent upon the amount of irradiation given. The first two groups consists of 20 cases, each of these patients was studied before and after one course of treatment received from one of two different roentgen-ray machines, delivering many long and some short wave lengths. Both of these machines represent types of apparatus which are commonly in use for therapeutic purposes at the present time. Of these 20 patients, 8 were given from one machine† and 4 from another‡ a smaller dose of roentgen-

* The clinical diagnoses were as follows: Carcinoma of breast, 18; of esophagus 3; of sigmoid, 3; of pancreas, 2; of prostate, 3; of testicle, parotid, tongue, palate, uterus, 1 each; hypernephroma, 2; mediastinal sarcoma, 2; 1 each of melanotic sarcoma, malignant tumor of chest wall (undiagnosed), sarcoma of fascia of thigh, retroperitoneal sarcoma.

In selecting this group of cases an attempt was made to exclude those in whom the hemopoietic system was obviously involved by malignant disease. Of course this does not mean that patients showing secondary blood changes associated with advanced malignant disease were excluded.

† Operated at 90,000 volts, a 9-inch spark-gap, and with the target placed 12 inches from the body of the patient.

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ray than that received from the latter apparatus by the 8 remaining individuals. The maximum dose given to any of the 12 former patients, who compose the first group, was 424 m.a.m., while the minimum dose was 144 m.a.m.; 3 mm. of aluminum and one sole leather filter was used. The treatment was given in two parts with an interval of four days between each part. The surface area of body exposed (portal of entry) was on an average 434 sq. cm.

The character of the larger treatments given the 8 patients who comprise the second group was as follows: The total dose varied between 630 and 1050 m.a.m.; 4 mm. of aluminum and one thickness of sole leather was used as a filter. The total treatment in each case was divided into four or five parts. In 6 of the 8 patients the total treatment was completed in the course of one week. In the other two, however, the total treatment was prolonged over two and a half weeks. The square body surface irradiated averaged 525 sq. cm.

The 22 patients composing the third group were studied before and after receiving 36 separate courses of roentgen-ray treatment from a new form of apparatus delivering great quantities of very short wave length roentgen-rays. This machine was operated at an equivalent voltage of 220,000 and the target placed 31 inches from the body of the patient; ½ mm. of copper was used as a filter. The total dose of any one course of treatment varied from 338 m.a.m. to 1950 m.a.m. Twenty-five of the treatments were given to 15 of these patients; each one of which was completed within a period of twenty-four hours and usually in less than seven hours. The remaining 7 patients received 11 treatments which were divided into four parts and given on four successive days. The surface area of the body irradiated averaged 940 sq. cm. for the 36 treatments.

The following blood examinations were carried out on each of the 42 patients comprising the three groups. Prior to irradiation, one and sometimes more determinations were made of the total and differential white cell count, red cell count, hemoglobin percentage and platelet count or estimation of the numbers of platelets. The detailed character of the formed elements was recorded. With the exceptions noted below these observations were repeated each day for six days following the conclusion of treatment.* The exceptions were that red cell and platelet enumerations were made daily on but 13 patients, and every few days on the others. After six days the patients were discharged from the hospital, and then the different blood examinations were repeated in most cases at least once each week, or four to five weeks or until the blood findings were similar to those observed prior to irradiation.

* "After-treatment," as used throughout this paper, means after the completion of treatment when it is given at one sitting. On the other hand, when the treatment is divided into four parts, the time "after-treatment" is taken from the completion of the second part.

The Blood of the First Group of Patients. The 12 patients of the first group who received the smallest dosage of all showed about a 20 per cent rise in the white count within the twenty-four hours following treatment. A further rise of 50 per cent during the next seventy-two hours was common. In no case was there a substantial decrease in the number of white blood cells during the period of observation. In some instances the white blood cells returned to their pretreatment level in seventy-two hours, while in others they remained above the pretreatment level for about ten days. The differential count showed no noteworthy changes except for a moderate reduction (20 to 25 per cent) in the number of lymphocytes during the first twenty-four hours. In one case the number of lymphocytes increased for one day. Following treatment the red blood corpuscles and hemoglobin showed no definite changes, but the platelets showed as a rule a slight rise. Degenerate changes of the white cells were frequently noted, especially in the polymorphonuclear leukocytes during the first five days following treatment. These fragmented white cells occasionally rose to as high as 15 per 100 formed white cells.

The Blood of the Second Group of Patients. The 8 patients of the second group who received more intensive treatment than those of the first group showed distinctly greater fluctuations in the white cell count than those receiving smaller doses. All of the 8 patients showed at least a 20 per cent increase, the maximum being 100 per cent, at the end of twenty-four hours following treatment. Following this rise, 2 cases showed no substantial decrease in the leukocytes, the count remaining elevated, in the neighborhood of 12,000 per cu.mm., as prior to treatment. After the transient rise, the white count of the other 6 cases then fell, reaching in three days a point below the pretreatment level. In 4 cases, leukopenia occurred, the white cells averaging 4500 per cu.mm., the lowest count recorded being 2600 cells per cu.mm. The leukopenia usually occurred on the third or fourth day following treatment, but in 1 case it developed as late as the ninth day. The duration of the leukopenia was from one to eighteen days, with an average length of about one week. The patients to develop leukopenia were those in whom the interval between treatments was shortest, and also in whom the total body surface exposed was greatest. When leukopenia did not occur, the pretreatment level of the white count was reached in one to two weeks, and when it did occur, it took about three weeks before the count returned to this level.

The differential white cell counts after irradiation in each of these 8 patients showed a distinct decrease of the circulating lymphocytes, often amounting to as much as a 50 per cent decrease. These cells began to drop immediately after the first part of the treatment, and remained decreased for a period of from two to three weeks, no matter whether leukopenia occurred or not. The poly-

morphonuclear neutrophiles were correspondingly increased in percentage. The other white blood cells showed no definite change in numbers. The blood platelets became definitely increased (33–100 per cent) during the first three days following treatment, and then returned to the vicinity of their pretreatment level. Changes in the character of the white cells were noticed, as in the cases of the first group who received smaller doses of irradiation. Degenerated white cells, to even as many as 20 per 100 perfect ones, were observed in the blood during the first week after treatment. The red cells and hemoglobin showed slightly irregular fluctuations but no constant changes.

The Blood of the Third Group of Patients Treated by Intensive Short Wave Length Roentgen-ray Therapy. The most particular information we have sought has been the effect of heavy irradiation—intensive short wave length therapy—on the formed elements of the blood, particularly the leukocytes. It was the third group of 22 patients that received 36 separate courses of such irradiation. The blood changes in these individuals were similar to, but decidedly more marked, than those observed in the second group. Greater blood changes carry more clinical significance than lesser ones, and those that occurred in this third group of patients are described and discussed below.

The White Count. During the first twenty-four hours following the intensive treatment of these patients there was a rise in the white count. This leukocytosis was transient and had usually run its course by the end of the first day when the white cells were 600 to 9000, usually 2000 per cu.mm; more than before irradiation. Then there occurred a sharp fall in the white count, so that usually on the second day it was below the pretreatment level. In all instances the count fell further, but more slowly, reaching on the average the lowest point on the sixth day following treatment. At this time, actual leukopenia (less than 5000 cells per cu.mm.) was present in 14 patients (63.6 per cent). Leukopenia occurred as soon as the second day in 2 cases, but the lowest level of the white cells was not reached until the fifth day. The white count of 1 case was at its lowest point as late as the twelfth day after treatment. This patient had a white count of 11,300 per cu.mm. before treatment and never showed an actual leukopenia. In 1 case the white count dropped to 2600 cells per cu.mm., and in 3 others was as low as 3200 cells per cu.mm. The duration of leukopenia was from two to thirty-one days, with an average of about nine days. Leukopenia occurred over fourteen days in 8 instances. However, the white count of at least 50 per cent of the cases did not return to the pretreatment level for four to five weeks.

In order to facilitate the study of the white cells after the 36 different courses of treatment given this third group of patients, the observations were divided arbitrarily into two groups: those

showing leukopenia (below 5000 white cells per cu.mm.), and those not showing leukopenia. The mean total white count and absolute number of the different white cells of the two groups are shown in Figs. 1 and 2. The first group comprises data obtained before and

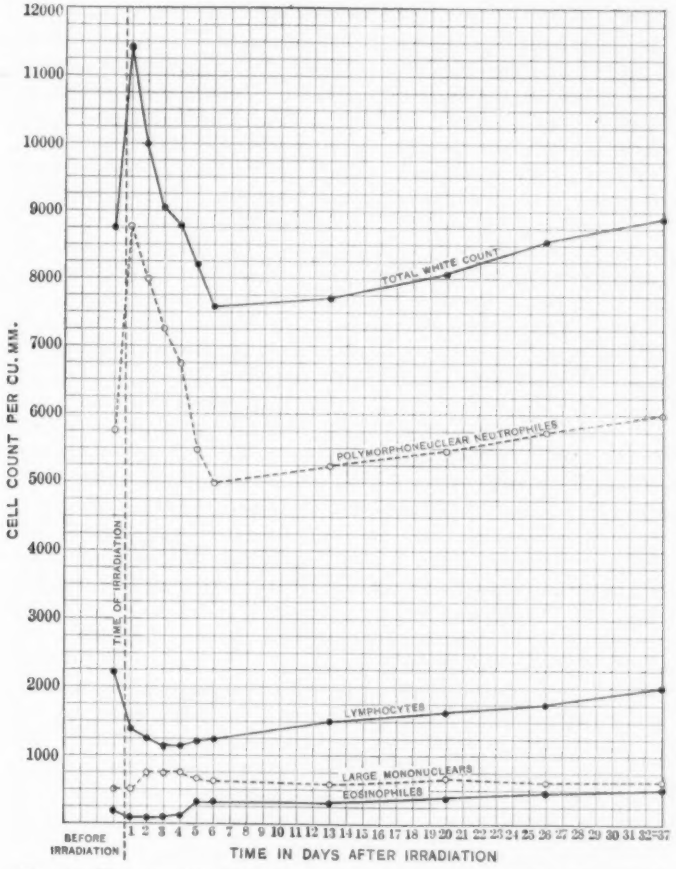

FIG. 1.—The mean total white count and absolute number of the different white cells per cu.mm. before and after twelve short-wave-length roentgen-ray treatments given 8 patients with malignant disease, who did not develop leukopenia.

after 24 courses of treatment given 14 patients, while the second consists of the observations before and after 12 courses of treatment administered 8 patients. The two figures show that in both groups the general trend of the curves for the total counts is the same, the variation being in the degree rather than in the character. Fluctu-

ations in the curves occurred in individual cases when the cause was obviously due to the primary disease or complications of the disease rather than the effects of irradiation *per se*. The pre-treatment counts of those patients showing leukopenia were lower than those

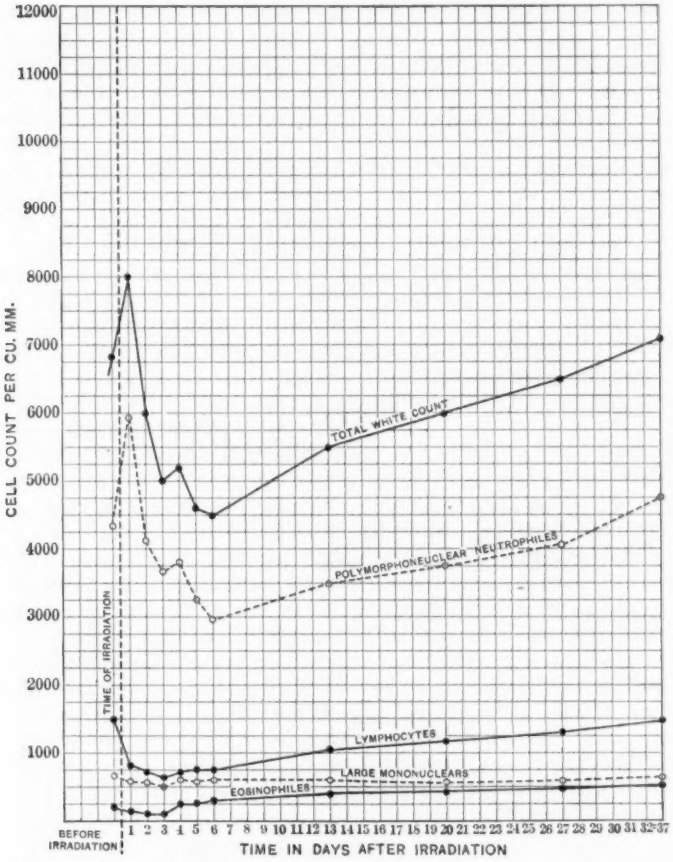

FIG. 2.—The mean total white count and absolute number of the different white cells per cu.mm. before and after twenty-four short-wave-length roentgen-ray treatments given 14 patients with malignant disease, who developed leukopenia.

in whom leukopenia was not produced. The height of the pre-treatment count may well be a factor in determining whether leukopenia will be produced or not. Even so, there are other and undoubtedly more important factors leading to the production of leukopenia that are to be considered later.

The data show that the effect of more than one treatment on the white cells depends not only upon the length of time elapsing between each course of treatment, but also upon the condition of the hemopoietic organs as reflected by the number of white cells present in the peripheral blood. If the white count has had sufficient time to return to its normal level, treatment of the same character as given before then produced changes similar to those occurring following the first treatment. If, however, second or third treatments were given before the cells returned to their original levels, leukopenia of greater degree and duration was produced. If a second or third treatment was given when the white count had just returned to normal, it appears from somewhat meagre data that leukopenia became more pronounced than if the normal white cell level had been established for some time. To 4 of the patients a second, and in one instance, a third, treatment was administered when leukopenia existed. In these instances the degree and duration of leukopenia was more marked than in any of the other cases; the lowest count recorded (2600 per cu.mm.) and the most persistent leukopenia (thirty-one days after the last treatment) occurred under these circumstances. No untoward clinical symptoms developed, however, following treatment given during leukopenia. Four cases (not included in the 22 of Group III) observed recently have received a second as well as a third treatment while leukopenia was present that developed following the first irradiation. All four have improved, and the white count is above 5000 per cu.mm. eight weeks after the last treatment.

The Lymphocytes. As Figs. 1 and 2 show, there was a prompt decrease in the number of circulating lymphocytes in practically every case of this third group. The fall was greatest during the first twenty-four hours, but continued for three days in nearly all the cases coincident with the decreasing white count. The lymphocytes usually remained at a low level for the next three days, and then rose very slowly for three to four weeks, rising proportionately more slowly than the white count. In three to four weeks they usually reappeared in normal numbers although at this time they were often below their pretreatment level. There were three instances when the lymphocytes did not decrease after treatment. However, in these instances the pretreatment level was low, evidently because a course of treatment had been given before. Occasionally the lymphocytes dropped from either a high or low normal percentage to a level of from 1 to 3 per cent, usually over a period of five days, but in 1 case within forty-eight hours. The degree of lymphopenia in this group of patients was distinctly more marked than usually observed in the other two groups who received less treatment and had less body surface exposed. A second or third treatment affected the lymphocytes in a similar fashion as the total white count. In some such instances when the

lymphocytes did not drop further, the persistence of their low level was of longer duration than usually seen after a first course of treatment. Likewise, as a rule, second treatments usually caused a longer duration of lymphopenia than leukopenia, and kept the lymphocytes low in proportion to the white count longer (sometimes weeks) than occurred following the first irradiation, so that lymphopenia is the last blood change to be readjusted. This only further indicates that the lymphocyte is the most sensitive cell to the rays.

The Bone-marrow White Cells. The curve of the polymorphonuclear neutrophiles follows that of the total white count very closely. The increase in the number of these cells seems to be responsible for the initial leukocytosis as the actual numbers of all the other cellular elements of the blood were either stationary or markedly decreased. During the period of leukopenia, the absolute numbers of polymorphonuclears were decreased, rarely as much as 50 per cent, though their percentage number was increased above normal.

Prior to irradiation in this third group of patients, the polymorphonuclear eosinophiles were never above 4 per cent. Following treatment, these cells decreased, as did other blood elements, for three or four days. However, these cells were seldom if ever absent from the blood even during the period of leukopenia. Following this primary decrease there occurred a relative and absolute increase of eosinophiles, usually starting at about the end of the first week and reaching a maximum during the second or third week after irradiation. Four of the patients showed respectively 9, 10, 12 and 23 per cent of eosinophiles, and 5 others had 5 per cent or over at some time during the second and third week following treatment. All but 3 patients showed 3 to 4 per cent of eosinophiles during this time, which was a greater number than was found in the first week after irradiation. The highest percentage of eosinophiles appeared in those patients who had received several treatments with the high voltage machine. One patient, who has received four separate courses of the short-wave-length treatment over the chest in the past fourteen months, has shown a slow but progressive increase in the number of eosinophiles, from 2 to 23 per cent.

Eosinophilia following irradiation appears to occur particularly as a result of repeated exposures, as shown by our observations and those recorded in the literature. This increase of eosinophil c cells does not seem to be related to the diseased state of the patient. An increase of these cells has been reported by others as occurring in those persons chronically exposed to radium and roentgen-ray, and we have commonly observed slight eosinophilia in such individuals. This information serves to further indicate that the eosinophilia observed after persistent therapeutic irrad at on is not necessarily due to disease.

The number and character of the polymorphonuclear basophiles showed no constant variation from the normal.

The absolute numbers of endothelial leukocytes (large mononuclear and transitional cells) were not changed to any appreciable extent after irradiation. Coincident with the rising white count they tended to be slightly increased (10 per cent). In 2 cases these cells were 12 per cent before treatment and continued elevated afterward, when there was a relative and actual increase of their numbers during the second and third week.

The Occurrence of Degenerated White Cells. The destructive or inhibitory action of irradiation on lymphatic tissue is reflected in the peripheral blood by lymphopenia, while its similar effect on the marrow is shown particularly by a decrease of the white cells derived from it. We have observed that large numbers of broken and degenerated white cells appear in the blood stream of man after irradiation, which further indicates the destructive action of the rays. The occurrence of such cells has been noted in animals, but scant reference has been made to their presence in man. Great numbers of such cells in many fantastic fragments and forms, together with increased ameboid activity of formed cells, are common following irradiation in cases of leukemia, but we have reference here to the presence of degenerated white cells in individuals not suffering from primary blood disorders. Such cells formed a distinct feature of the blood in all the 36 patients of the three groups but particularly in the 22 patients treated intensively with short-wave-length therapy.

The destruction does not seem to be limited to any one variety of cell. Many, however, were so degenerated that proper classification was impossible. The greatest number of these cells appear during the first three days after treatment and slowly diminish in number during the next three days, but do not reach a normal level until the second or third week following irradiation. They occurred most profusely when leukopenia and lymphopenia were marked, although they were repeatedly observed in patients with slight changes in the numbers of white cells. It was common to find in the third group of patients 25 to 30 of these cells per 100 formed white cells during the first three days following irradiation. In one there were 50 degenerated cells per 100 formed white cells observed within the twenty-four hours following treatment. Thus the numbers of such cells observed after the larger doses of irradiation given the third group of patients were greater on the average than the numbers seen after the smaller doses given the patients of Groups I and II.

The Presence of Immature White Cells. Besides the histological features of the white cells indicative of premature death, a second form of histological change, little commented on in the literature, was observed in these cells after irradiation. This consists of signs indicative of youth. Youthful polymorphonuclear cells (uni- and bilobed neutrophile polymorphonuclears with often rather coarse granules) from the marrow began to appear in abnormal numbers

about four days after irradiation, particularly in patients of the third group, but also in those of Group II. No greater numbers were observed whether leukopenia was present or not. The occurrence of these immature forms persisted approximately until the white count returned to its pretreatment level. It was common to observe from 3 to 5 per cent of such cells, and 10 per cent represents the maximum number. The greatest number occurred shortly following the time that the white count was at its lowest point. Immature forms of large mononuclears were also observed during the period of leukopenia. The presence of distinct increases of immature lymphocytes was not observed. Occasionally a few atypical mononuclear cells appeared that may well have been immature forms of lymphocytes. No myelocytes were observed. The occurrence of these youthful cells simply indicates that following the inhibitive action of irradiation, normal, orderly regeneration occurs. Their absence, however, should not necessarily be taken to indicate an unfavorable feature.

The Blood Platelets. Immediately after the intensive treatment given this third group of patients, the blood platelets often showed a transient increase in their numbers. Then a slight decrease for a few days occurred; by count, seldom more than 75,000 per cu.mm. In 1 patient, the platelets decreased to the vicinity of 100,000 per cu.mm. when the white count was about 3000 per cu.mm. These elements derived from the megacaryocytes of the marrow appeared to be depressed less readily than the leukocytes, though following repeated exposure their number may become so few that a state of chronic purpura hemorrhagica exists, as observed in some roentgen-ray workers. In this third group of patients, about the fourth day after irradiation, usually some days prior to a definite rise in the white count, the platelets increased so that in a few more days they were commonly found in greater numbers than normal. Increased numbers were then observed for a few days to a few weeks. The increase though definite (usually 125,000 per cu.mm. above normal) was seldom marked. More marked changes in their numbers and character do, however, occur following heavy irradiation in some cases of disease of the hemopoietic tissue. No noteworthy changes in the character of the platelets were observed in any of the 36 patients.

The Red Blood Corpuscles and Hemoglobin. No characteristic or constant changes in the number of red blood corpuscles and hemoglobin percentage were observed in these patients irradiated intensively, the same being true for those of Groups I and II. There is no question that fluctuations in the number of red blood cells and hemoglobin occur as the result of irradiation as shown by numerous reports, particularly the more recent ones, as well as by the observations we have made. However, neither increases nor decreases occurred with any constancy in our patients. We can

record in the first few days after treatment both increases and decreases of 500,000 red cells per cu.mm., while no cases showed as great a variation as 1,100,000 per cu.mm. during this period of time. It would seem that the therapeutic doses given, tended more often than not, to permit a transient slight decrease in the red blood cells for a few days after treatment. As noted above, excessive irradiation can lead to distinct anemia, but even many repeated intensive doses given at intervals of more than six weeks have not led to anemia. In fact, 2 cases in our series that received four courses of treatment showed not a decrease but a progressive marked increase in the red count. This is to be attributed to the effect of irradiation in decreasing the activity of the condition that was responsible for the anemia. Those patients that were distinctly anemic* before treatment did not have any greater changes in their red cell count or white cells soon after irradiation than those without anemia. No definite histological changes in the erythrocytes were observed which could be attributed to irradiation. Fluctuations in the numbers of immature red cells, that tend to parallel the numbers of white cells, do occur and will be reported upon by Dr. Isaacs of this clinic.

Consideration of the Cause of the Degree of Leukopenia and Lymphopenia. It is evident from the observations recorded above, as well as those in the literature, that the new short-wave-length roentgen-ray therapy, when properly used, produces no changes in the blood that are of a different character than those occurring after milder yet intensive therapy from other forms of apparatus or radium; nor changes that are serious for the patient, provided they are not ignored. It is clear that the most important blood changes are leukopenia and lymphopenia. The changes in the white cells that occur following irradiation tend in general to vary in direct proportion with the size and intensity of the dose, so that large doses of short rays are more effective in producing leukopenia and lymphopenia, than large doses of long rays, and greater rather than smaller doses of either cause a more distinct effect on the white cells.

The portion of the body irradiated does not appear to importantly influence the degree of alteration in the white cells. It has been our impression that irradiation of the abdomen might lead more often to a rapid and longer lasting leukopenia and lymphopenia than irradiation elsewhere. However, our data and those in the literature do not clearly indicate such to be the case. Petersen and Saelhof's studies do suggest that if the abdomen is exposed greater blood changes occur than when irradiation is applied elsewhere.

In our cases, however, the degree and the duration of the changes in the white cells have varied within wide limits when the amount

* In this series 1 with 50 per cent and 4 with about 60 ger per cent hemoglobin. In addition 4 cases recently observed with 25 to 50 per cent hemoglobin.

of treatment as measured by purely physical standards indicating size and intensity of dose has been the same. Some of the patients receiving the largest doses did not have leukopenia, while some of the instances of profound leukopenia occurred following doses half the size of the maximum dose.

Recognition must be given to the fact that the influence of any substance on the blood will be modified by the state of the individual's hemopoietic organs, which owing to disease and its complications will vary in different patients. It was recorded above that the initial height of the total number of white cells and lymphocytes might play a role in determining the degree and duration of their decrease following irradiation. Our data show no further distinct correlation between the clinical condition of the patient with malignant disease: including the amount of anemia present, (even with hemoglobin 50 per cent) and the amount of alteration observed in the white blood corpuscles after irradiation.

It is clearly evident that the size and intensity of ray dosage is a much more important factor in the production of leukopenia and lymphopenia than any state of the patient. There is, however, another factor of importance as shown by Levin's[32] work on animals, but which heretofore has been neglected in the clinic. This factor is the amount of surface area irradiated. An analysis of our data shows that the intensity and duration of the leukopenia and lymphopenia is on the average in direct proportion to the square surface of the body exposed to the rays, that is, their portal of entry. Thus one would expect that a large dose applied over a large area would produce a more profound effect on the formed blood elements than a similar large dose applied over a small area, and such is borne out by our observations. In both instances the leukopenia and lymphopenia may become of the same degree, though usually more marked with the greater portal of entry of the rays. However, the duration of the white cell changes will always last longer when the radiation is over a larger rather than a smaller area. Table I summarizes the data concerning the effect of dosage* and the portal of entry of the rays on the white cells.

The amount of secondary radiation produced in a patient is proportional to the three chief factors: The size of the dose, the wave lengths administered, and the size of the portal of entry, factors that determine the amount of reaction the white cells will show, exclusive of inherent differences in patients themselves. In some cases this secondary radiation amounts to as much as 40 per cent increase in the size of the dose administered by the short wave length machine used to treat the patients of the third group. This

* The dose measured in electrostatic unit seconds is approximately comparable to that measured in milliampère minutes. Data for the former are not available for this whole series of cases. About one thousand electrostatic unit seconds were given those patients more recently treated with the short wave length apparatus.

phenomenon indicates how the actual dosage becomes bigger not only with shorter than longer wave lengths but also with a larger portal of entry. One might consider that this additional radiation accounted for the greater degree of leukopenia and lymphopenia observed when a greater rather than a smaller area was exposed. This secondary radiation is probably an important factor, even so the direct exposure of a greater amount of blood and tissue as occurs with a larger portal of entry probably plays a role in the production of the blood changes.

THE RELATIONSHIP BETWEEN THE ROENTGEN-RAY DOSE, THE SURFACE AREA OF THE BODY EXPOSED, AND THE ALTERATIONS IN THE WHITE BLOOD CORPUSCLES.

Group.	Number of courses of treatment.	Roentgen-rays.	Average dose in milliampère minutes.	Average sq. cm. of body surface exposed.	Alterations in white cells.
I . .	12	Chiefly long	250	434	Very slight.
II A.	4	Many long and some short	800	331	Slight; no leukopenia.
II B.	4	Many long and some short	945	678	Typical; brief duration; leukopenia.
III A.	12	Many short	1090	665	Typical; moderate duration; no leukopenia.
III B.	24	Many short	1020	1050	Typical; long duration; leukopenia.

The Clinical Significance of the Blood Changes. The biological reaction of the white cells produced by irradiation has clinical significance. It may perhaps give information regarding the future state of the patient, and does aid to determine the dose of irradiation, particularly for individuals previously treated. Claims have been made by Westman,[69] Maseiri,[35] and Heim,[21] for example, that cases favorably affected by the rays show less pronounced blood changes after irradiation with more rapid restoration, especially of the lymphocytes, than refractory cases. We have not at hand sufficient data to prove or disprove this assertion. However, among our cases are some who had marked and prolonged leukopenia and lymphopenia, and who appeared to be definitely benefited by treatment, more so than some others who did not present such profound changes in the blood. Whether greater benefit would have occurred if irradiation had been given without producing as marked blood changes is problematical.

It is possible that this biological reaction of the hemopoietic tissue might serve as a measure for determining the most suitable dose of irradiation, because like doses measured by physical methods

produce different effects, not only on similar tumors in different patients, but also different degrees of depression of hemopoietic tissue. A study of many cases will be necessary in order to predict the exact influence on the blood of a given dose in a given case. It would be interesting to study the degree and character of improvement of a large series of cases to whom intensive treatment was given without producing leukopenia and but transient lymphopenia as contrasted with a similar series of cases where treatment permitted distinct blood changes for some time. The patients whose white cell counts are averaged in Figs. 1 and 2 perhaps give such a comparison. But the data are too meagre to draw from them conclusions of this type. There is at least a suggestion that those cases not showing leukopenia did better than those that did. Others, as noted above, have reported the same.

Neither our data nor those of the majority of others show that there is any relationship between the amount of "roentgen-ray sickness" and alterations in the formed blood elements.

Depressed activity of the marrow as shown in the peripheral blood by leukopenia with a decrease of the bone-marrow white cells as well as decrease of the platelets and immature red cells must be looked upon as an undesirable state. Likewise lymphopenia indicative of decreased lymphoid activity is an undesirable condition in many instances. It has been pointed out that increases of lymphocytes may favor immunity to cancer,[46, 47, 48] so that on this account alone a decrease of these elements is not ideal. Even so, leukopenia and lymphopenia may occur without there being any obvious detrimental effect, and in the effort to treat the patient most adequately the production of such blood changes may be an unavoidable circumstance. They are also of much less importance than the amount of benefit obtained from doses causing depression of hemopoietic tissue. One cannot believe, however, that it is wise to produce marrow and lymphoid depression for a considerable period of time. In so doing, a tumor may be markedly decreased, but to obtain such a result the hemopoietic system might be so severely injured as to function very inadequately. Ideally one would like to be able to obtain the effect upon malignant disease given by intensive irradiation without producing depression of hemopoietic tissue. At present this does not appear easy to accomplish, and our data, as well as those of others, show that the relatively transient depression of the hemopoietic tissues is not alarming. In fact, treatment may be given in the face of leukopenia without necessarily any disturbing circumstances arising. One must bear in mind, however, that repeated doses may cause an increasingly greater degree and duration of depression of the marrow. The effect is quite comparable to other marrow reactions; for example, that observed after recurring blood loss.[18] Following one hemorrhage many young red cells appear in the blood stream and

the red count soon returns to normal, while following an equal amount of blood loss after repeated hemorrhages the young forms increase less and the numbers of red cells return more slowly to normal.

It is certainly very desirable to examine the blood before any irradiation treatment, particularly when intensive irradiation has been given before. A white count alone will usually suffice for practical purposes. If the count is found normal or elevated, there is no question but that treatment may be given without any fear of doing harm to the hemopoietic tissues. If this count has only just returned to normal following depression from previous treatment, a greater or more lasting depression will occur than if the cells had been established at a more normal level for some time. This should be recognized if one desires to give treatment without creating depression of the hemopoietic tissues. Also the effect of disease itself on the blood picture is to be taken into account when one is evaluating analyses. Though treatment may be given in the face of leukopenia without any inherent danger, it is probably wiser not to do so; becoming a more serious event each time treatment is repeated in the same case under such circumstances. Thus, in deciding whether or not to treat a patient with leukopenia, one must attempt to decide if the disease has reached such a state that treatment of it is desirable, in spite of the creation of an increased depression of the hemopoietic tissue. This latter condition may become of relatively little importance and be distinctly less harmful than permitting the lesion to go untreated. Before it is finally decided to give treatment when leukopenia is present, further blood examination should be made, because this may reveal a more serious depression of the marrow than a white count alone. For example, if under such circumstances the blood platelets are found to be distinctly reduced it would indicate a much more profound depression than if they were not; then treatment might possibly cause a serious effect.

It is conceivable that it is of greater importance to consider the absolute number of lymphocytes present before irradiation of cancer than the total white cell count. To do so requires additional time and it does not seem essential to obtain this information, though when treatment of diseases of the lymphatic tissue is being considered, a careful histological study of the blood should supplement the white count. In comprehending the effect of therapy one must bear in mind how it acts on lymphocytes, because if one could permit them to remain elevated and at the same time favorably effect the lesion to be treated, it probably would be beneficial.

Some have considered that the development of an eosinophilia is a favorable finding for prognosis. Such may be the case in spite of the fact that it seems to be a result particularly of repeated exposures.

There appears to be no further particular clinical significance to be attached to other alterations in the formed elements of the blood than those discussed above, including the fact that no important relationship has been found between the patient's future clinical state and the number of degenerated white cells appearing in the peripheral blood after irradiation.

So that confusion shall not arise, it is pointed out here that the cases reported upon in this paper and the discussion given does not refer to patients with fundamental disease of the bone-marrow or lymphatic tissue. The evaluation of blood examinations must be taken differently when considering irradiation in many such patients.

Summary. 1. The literature concerning the effect of irradiation on the formed elements of the blood is confusing. A review and essentially complete bibliography is given.

2. A study has been made of the blood of 42 cases, chiefly of cancer, before and after 56 roentgen-ray irradiation treatments. Particular attention was given to the observations on 22 of the patients given 36 intensive short wave length treatments. The other irradiations were milder. Cases of disease of the hemopoietic tissue are not included and the statements below require modification when applied to such conditions.

3. The most important effect of customary therapeutic doses of irradiation on the blood elements is to decrease the number of white cells, especially lymphocytes, so that leukopenia and lymphopenia may occur. Preceding the decrease in the white count a transient increase develops, due to increment of polymorphonuclear neutrophiles. Very small doses of irradiation may permit a lymphocytosis.

4. When a customary therapeutic dose of short wave length roentgen-rays is given, it causes the white count to reach its lowest point about six days later; at that time leukopenia (a count below 5000 per cu.mm.) is more often present than not. A decrease below normal of the absolute numbers of bone-marrow white cells, which is indicative of marrow depression, is not unusual. Leukopenia lasts on the average about nine days, but may persist for over four weeks. Even if the white count remains above 5000 per cu.mm., the white count often does not return to its pretreatment level for a month. If treatment is given again before the number of cells have remained for some time at their original level, leukopenia of a greater degree and duration is produced than after the first treatment.

The fall in the lymphocytes is greatest in the first twenty-four hours, but they continue to drop for about three days. These cells rise with the white count, but do so proportionately more slowly. Subsequent treatments may keep the lymphocytes fewer in proportion to the white count than following the first irradiation.

5. The new short-wave-length roentgen-ray therapy, suitably given, produces no changes in the blood that are of a different character from those occurring after milder yet intensive irradiation.

However, it does produce more rapid, marked and persistent changes than milder treatment, and if the treatment consists of merely moderate long-wave exposures it may not even cause a decrease of white cells.

6. An eosinophilia, of often 7 and as high as 23 per cent, is usual two to three weeks after short-wave-length irradiation. It appears to develop particularly following repeated exposures.

7. After irradiation the blood contains many degenerated white cells, especially in the first three days. There is scant mention in the literature of this feature of the blood in man. Larger doses produce greater numbers of these cells than smaller doses. After short-wave-length therapeutic irradiations the degenerated cells often amount to 25 per 100 formed white cells.

8. Some increase of immature white cells may be observed, especially at about the time the white count begins to rise, after large doses of irradiation.

9. A slight increase of the platelets soon after irradiation is common. They are depressed less readily than the white cells, but following the transient rise they are often found slightly decreased and rarely markedly. Combined with leukopenia they may be an indication of greater marrow depression than a decrease of only the bone-marrow white cells. About four days after intensive irradiation and prior to a definite rise in the white count, the platelets rapidly increase and remain elevated above normal for days to weeks.

10. Important changes in the count of the red blood corpuscles and hemoglobin percentage do not occur as a result of mild or intensive therapeutic irradiation. Changes in the numbers of immature cells occur.

11. The clinical condition of the patient will influence the degree and duration of the blood changes after irradiation, but anemia *per se* does not seem to be of any great importance. The white cells of patients whose clinical condition is similar, given the same dose in the same manner, show considerable variation. On the average, patients with higher white counts before irradiation will develop leukopenia and marked lymphopenia less often than those with lower counts.

12. Much more important than the condition of the patient in determining the influence of irradiation on the blood is the size, intensity and character of the dose; larger doses producing greater blood changes than smaller ones.

13. The amount of surface area irradiated is a factor of great importance in determining the degree and duration of the decrease of white cells. The greater the surface area exposed to a given amount of irradiation the more profound, on the average, is the effect on the white cells. Secondary radiation, which is greater with larger than smaller doses, with short wave than long wave

lengths, and with a larger than a smaller portal of entry, probably plays a role in the production of the blood changes.

14. Depression of the activity of lymphatic tissue and bone-marrow are probably undesirable states, yet may occur for even weeks after irradiation without any obvious detrimental effect. In spite of the production of leukopenia and lymphopenia, the benefits derived from radiation appear to offset these changes.

15. Prior to irradiation, particularly if one dose has been given, the blood should be examined. A white count alone will usually suffice to indicate the state of the hemopoietic organs. If 5000 per cu.mm. or more, irradiation may be given without producing serious harm to the blood forming tissues. It is not ideal to give irradiation when leukopenia is present, but it may be done without disaster. With leukopenia, especially when marked, repetition of treatment probably becomes a more serious event.

16. Before treatment is given to a patient with leukopenia, a complete study of the formed blood elements should be made, for it may reveal a greater degree of marrow depression than that shown by leukopenia only, and thus induce one to decide against irradiation. In order to determine whether or not to treat a patient with a given degree of leukopenia, one must decide whether the benefits of treatment will offset the disadvantages of an increased depression of the hemopoietic tissue. This latter condition may become of relatively little importance and be distinctly less harmful than permitting a lesion to go untreated.

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PRIMARY CARCINOMA OF THE LIVER.

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In 1876 Kelsh and Kiener[1] reported 2 cases of primary carcinoma of the liver, and at that time found only one other case in the literature. Next Sabourin[2] added 4 more cases, but the first thorough investigation on the subject was done by Hanot and Gilbert[3] in 1888.

According to the gross appearance, the French pathologists classified the tumor as:

1. "Cancer Nodulaire," in which the liver contains several tumor nodules varying in size and generally well circumscribed.

2. "Cancer Massif," in which the tumor consists of one large mass occasionally associated with metastases.

3. "Cancer avec Cirrhose."

Eggel[4] in an investigation of 163 cases accepts the same macroscopical classification except for the "cancer avec cirrhose" which

he calls "cancer à forme diffuse" on the ground that cirrhosis is often found in the nodular as well as in the massive form.

Histologically, Eggel[4] classifies each of these groups into the solid and adenomatous carcinomas. Ribbert[5] differentiates trabecular and alveolar types. Goldzieher and Bokay[6] divide the tumor into "Carcinoma Hepatocellulare" and "Carcinoma Cholangiocellulare" *according to the cells from which they arise;* viz., liver cells or epithelium of the smaller bile ducts. This nomenclature was later modified by Yamagiwa[7] as "Hepatoma"* and "Cholangioma."

The incidence of the tumor is rare. Eggel[4] in a review of the literature up to 1901 reported 163 cases and 1 case of his own. Among the 163, only 117 were studied histologically. In 258 cases of cancer of the liver, Hansemann[8] found 4 in which the liver was the primary seat of the tumor, Goldzieher and Bokay[6] reviewed (1911) 6000 autopsies at the Pathological Institute of Budapest and found 18 primary cancers with an incidence of 0.3 per cent. (The highest figure ever reported.) Winternitz[9] discovered at the Johns Hopkins Hospital only 3 cases of primary cancer of the liver in 3700 autopsies, an incidence of 0.028 per cent. Recently, Clawson and Cabot[10] reported 1 case which is the only one in a total of 5100 necropsies performed at the University of Minnesota. At the Peter Bent Brigham Hospital, we found 4 primary carcinomas (3 cholangiomas and 1 hepatoma) of the liver in 1200 autopsies performed in the past ten years. At the Harvard Medical School only 1 case (cholangioma) has been seen in autopsies.

The cases reported were referred to me by Dr. S. B. Wolbach and belong either to the Harvard Medical School or to the Peter Bent Brigham Hospital. I desire to express my deep gratitude to Dr. Wolbach for his permission to study the cases, his kind suggestions, and criticisms.

Case Histories. CASE I.—CLINICAL HISTORY. S. H., a female, aged sixty-three years, entered the Peter Bent Brigham Hospital complaining of swelling of the abdomen with pain.

Family and Past History. Not remarkable.

Present Illness. Five weeks ago she noticed that her abdomen began to swell, accompanied by severe pain all over the abdomen and constipation. During this time she lost weight, and two weeks ago there was swelling of the legs and shortness of breath, and recently nausea and vomiting.

Physical Examination. Shows dulness at the bases of both lungs with diminished vesicular breathing on the left side and diminished bronchial breathing on the right side. There are numerous rales at both bases. The abdomen is tremendously dis-

* The term "hepatoma" was originally employed by the French writers, Rènon, Giroudel and Monier-Vinard in the article L'hépatome tumeur primitive du foie, Arch. de méd. expérim., 1910, **22**, 311.

tended. There is marked edema of the legs and the lower half of the trunk. Pelvic and rectal examinations are negative.

The patient was tapped twice, 5000 cc and 4100 cc of fluid being obtained. The specific gravity of the fluid was 1008 and a differential count showed 352 cells, 7 per cent of which were polymorphonuclear leukocytes and 85 per cent lymphocytes. The blood Wassermann was double plus. The leukocytes were 19,000 per c.mm.

Clinical Diagnosis: Cirrhosis of liver, probably luetic.

Autopsy (A-21-118) was performed by Dr. S. B. Wolbach and Dr. W. S. Quinland.

Body: Not remarkable on general inspection, except for a protuberant abdomen and the presence of two paracentesis wounds in the median line and in the right flank respectively.

Peritoneal Cavity: Contains 1800 cc of bile tinged fluid in which are several flecks of fibrin that measure roughly 4 to 5 cm. in length. This fluid when stained is found to contain endothelial cells and polymorphonuclear leukocytes with a few phagocyted bacilli having the morphology of colon bacilli. There are a few fibrous adhesions in the region of the ileocecal junction. The appendix is very small and appears to be somewhat atrophic. It is bound down posteriorly to the cecum by fibrous adhesions. The height of the diaphragm reaches the lower border of the fifth rib on the left and the fourth rib on the right. The mesenteric lymph nodes are not remarkable.

The pleural and pericardial cavities are not remarkable.

The heart weighs 260 gm. and except for a tortuosity of the vessels is not unusual.

The lungs weigh (right) 390 gm. and (left) 330 gm. They are similar in appearance, and except for a hypostatic congestion are not remarkable. Along the surface and adjacent to the interlobar septa on the right and the interlobar septum on the left are a few whitish elevations in what appears to be lymphatic vessels that suggest tumor metastases.

The spleen weighs 210 gm. and shows chronic passive congestion.

Gastrointestinal tract: The stomach contains about 16 cc of "coffee-ground" material. The mucosa has a few pin-head sized areas of depression, suggestive of autodigestion. At a distance of 5.5 cm. from the pyloric orifice in the duodenum is a definite ulcer of about 7 mm. in diameter, the base of which rests on the head of the pancreas. The borders are regular and smooth, and the surface in general appears dark red. In this same region but on the anterior wall of the duodenum is a similar ulcer that has perforated the wall of the gut.

The pancreas is normal.

The liver weighs 1820 gm. and is practically replaced by a tumor which is more evident in the left lobe. Here the liver tissue is entirely replaced by tumor and the organ in this region is dense

and of cartilaginous consistency. Toward the mesial portion, patches of liver tissue are seen that measure roughly 3 cm. in diameter and on the under surface of the right lobe the largest patch of liver tissue is seen (about 10 cm. in diameter). The surface of the organ is irregularly indented, the tissue being pulled down, having little wrinkles on the surface. On section the appearance is well mottled in the right portion but more homogeneous on the left side where the tumor is more diffuse.

The gall-bladder is normal and the ducts are patent.

The kidneys are similar in appearance. The right weighs 130 gm. and the left 140 gm. The capsule strips easily from both organs, leaving a dark red, finely granular surface. On section through the left kidney a few pin-head sized tumor metastases are seen in the region of the medulla. The cortex is regular and appears normal. The glomeruli and pelves are normal.

The adrenals are normal.

The bladder is normal.

Except for a small fibroid the uterus is not remarkable, the ovaries and tubes are of the senile type.

The aorta shows a few atheromatous plaques in the abdominal portion.

The thyroid and parathyroid glands are dissected after the tongue and trachea have been removed. No evidence of tumor is observed.

Microscopical Examination. Liver: Sections are stained with methylene blue-eosin, with phosphotungstic acid-hematoxylin and with Mallory's anilin blue. They all show areas of tumor consisting of cuboidal epithelial cells. The cytoplasm of the cells is stained with a basic stain, is clear and is not abundant. The nucleus is ovoid or round, vesicular and contains a deeply stained nucleolus. The arrangement of the cells is in general adenomatous with a tendency to form small ducts. The larger masses of tumor seem to be generally confined to the portal areas and it is from these areas that they spread and extend into the liver substance. In the center of some tumor masses, the bile duct of the portal area can still be made out. In general, the portal areas contain an increased amount of fibrous tissue which is dense around the bile ducts. The latter are everywhere hyperplastic, their lining epithelium being of a tall variety, and in areas consisting of 3 to 4 rows, forming folds into the lumen. Tumor growth is present in the capillaries in the portal areas. Mitotic figures are frequent. The stroma of the tumor in the large as well as in the smaller nodules consists of connective tissue which in areas is very abundant.

The tumor ends rather diffusely in the surrounding liver substance which shows a marked distention of the sinusoids by serum and red cells (edema and congestion). The liver cells themselves being arranged normally show, however, some changes; their nuclei are pyknotic in proximity to the tumor and the cells are compressed and atrophic.

Lungs: The tumor here is made up of the same type of cells and has a similar arrangement as in the liver. It is located in the interlobar septa and in some perivascular spaces. The stroma is fibrous. The adjacent normal lung substance is compressed. There is congestion and a moderate amount of anthracosis. The bronchioles are not remarkable.

Spleen: The histology is that of a chronic congestion.

Pancreas: Shows polymorphonuclear leukocyte infiltration of the interlobar septa and lobules. A few thrombosed vessels are seen. There is no evidence of tumor.

Duodenum: Sections show in one portion necrosis of the mucosa and submucosa with very little inflammatory reaction. A few polymorphonuclear leukocytes are seen in the muscle coat. The stomach is normal.

Kidneys: Sections show congestion and an accumulation of blood in some of the straight tubules. One of the sections shows a circumscribed area of scarring in which epithelial cells are scattered loosely. There is a slight thickening and retraction of the glomerular tufts, also a few areas of scarring in the cortex.

Adrenals: Normal.

Genitalia: Normal.

Thyroids and parathyroids: Normal.

Microscopical Diagnosis. Carcinoma of liver with metastases to lungs and kidneys; ascites; duodenal ulcer, perforating; chronic passive congestion of spleen; edema of extremities; arteriosclerosis.

Case II.*—Clinical History. E. P., an unmarried seamstress, aged sixty-one years, entered the Peter Bent Brigham Hospital complaining of an increasing sense of "tightness" in the chest, some "wheezing" on breathing, progressive dyspnea, occasional slight hemoptysis and insomnia. Associated with these complaints were increasing weakness and loss of weight of about 20 pounds. According to her statement she had been sick for one month.

Family History. Her father and both paternal grandparents died in middle age of pulmonary tuberculosis.

Past History. She had had measles at six, "intermittent fever" at sixteen, and malaria at forty-six; hysterectomy and oöphorectomy ten years ago, following vague pelvic symptoms. She was told that gall stones were found in her gall-bladder, but that her condition prevented further investigation.

Physical Examination. The chest showed questionable small areas of dulness posteriorly, most marked in the region of the hila Fine crepitant rales were heard through the left lung and there were a few fine moist rales at the right base, behind and over the right lower chest anteriorly. The abdomen is negative, except for an

* This case was reported from the clinical point of view by R. M. McKean in Amer. Jour. of Med. Sci., 1922, **163**, 710.

increased resistance to palpation in the epigastrium and right hypochondrium. An underlying mass, the character of which could not be determined on account of the rigidity of the abdominal musculature. The liver dulness extended from the sixth rib above to three finger breadths below the costal margin.

Heart, Gall-bladder, Spleen and Kidneys. Not remarkable.

Roentgen-ray showed a "spotty" consolidation throughout both lungs, most marked in the lower lobes. This consolidation has every appearance of being metastatic malignancy and not tuberculosis. The blood Wassermann was negative. Gastric analysis showed a normal acidity curve. The sputum was repeatedly negative for tubercle bacilli. Stool and urine examinations were negative. The patient remained in the hospital for forty-seven days and died apparently of respiratory failure.

Clinical Diagnosis. Metastatic malignancy of the liver and lungs. Primary source undiscovered.

Autopsy (A–20–108) was performed by Dr. V. Jacobson.

General examination of the body is negative.

There is no free fluid in the peritoneal cavity. The omentum is firmly adherent to the peritoneum along the line of the abdominal scar. The liver is very prominent, being pushed downward and forward, its lower border being 15.5 cm. below the xyphoid cartilage and 7 cm. below the right costal margin. The spleen is covered by the left lower ribs. The appendix is not present. A short cervical stump remains. The diaphragm is on a level with the lower border of the third rib on the right and with the fourth rib of the left. The mesenteric lymph nodes are very small and are embedded in much mesenteric fat.

The pleural cavities are almost obliterated by the adhesion of the lungs to the parietal pleura which is rough and nodular, due to the presence of innumerable, irregularly rounded projections of tumor, varying in size from a pin-head to one on the diaphragmatic pleura which is 3 x 2 x 3 cm. These nodules are dark red, streaked with white, very firm and unusually surrounded by radiating dilated veins. In the right cavity, 250 cc of blood-tinged fluid and in the left 150 cc of similar fluid is found.

In the mediastinum, the under surface of the sternum is studded with tumor nodules 0.2 to 2 cm. in size. The mediastinal fat is of normal amount and shows no tumor growth. The organs are in normal position.

The pericardial cavity and heart are normal.

The lungs weigh (right) 710 gm. and (left) 705 gm. They are quite similar in appearance, about half the normal size, but much increased in weight. The pleural surfaces are rough and nodular, due to the presence of innumerable, rather hard, pale white, circumscribed growths, varying in size from 1 mm. to 2 cm., projecting about 3 mm. above the surface. They are found all over the pleura, and while

the lymphatics are fairly prominent, these tumors do not seem to be intimately connected with them and about many are radiating, dilated venules. Between these bodies the tissue is rather elastic and is slightly crepitant and grayish-red. The glands at the hili and also at the bifurcation of the trachea are 1 to 2 cm. in size, many are very firm and on section are opaque white, streaked with red. A lateral incision in each lung shows a widespread distribution of tumor nodules, similar to those on the pleural surfaces. They vary in size as in the pleura and are diffusely distributed in the lung lobules. Many are stained with carbon pigment or surrounded by a narrow black ring of anthracosis. The tissue between the tumor varies in color from gray to deep red and in consistency from elastic to firm and meaty. Thrombi occlude many of the arterioles but the larger vessels are empty. In some of the bronchioles are dark red blood clots in which are small particles of opaque white tissue suggesting tumor. The trachea shows moderate injection of the mucosa.

The liver weighs 2360 gm. It is much enlarged, particularly its right lobe, which on its lateral and posterior surfaces is firmly adherent to the diaphragm. This is due to the presence of a tumor mass occupying about half of the right lobe and extending outward so that a mass with pearly white, raised borders and dark red, depressed central portion projects about 1 cm. above the surface over an area about 12 cm. in diameter, forming a growth, shaped more or less like a group of rosettes. The diaphragm appears to be invaded, and streaks of grayish-white tumor tissue run from the liver tumor to the large nodules on the pleural surface of the diaphragm.

Sections of the liver at various angles show that the gross tumor is limited to the large mass in the right lobe, the rest of the organ having only a moderate "nutmeg" appearance. It is fairly well circumscribed and its greatest diameter is 15 cm. It is of almost cartilaginous hardness and has no definite capsule, though with rounded edges. There is distortion of the liver lobules adjoining it, probable due to pressure. The tumor is not bile stained and there is no gross evidence of bile stasis. Dissection of the larger bile ducts leading to the tumor is abruptly stopped when the tumor is reached. Small branches of the hepatic vein contain thrombi in the vicinity of the tumor, and a few of them contain flecks of grayish-white, quite firm tissue, possibly tumor. The ducts and vessels of the rest of the liver show no lesions.

The gall-bladder is but 5 cm. from the tumor but its mucosa moves freely over the subjacent tissues and appears normal. Eight black facetted calculi, 1.5 cm. in size, lie free in the gall-bladder. The cystic, hepatic and common ducts in the porta hepatica show no stones or tumor. Two lymph glands at the junction of the cystic and hepatic duct are enlarged and firm, measuring 2 x 5 cm. in size, but are pale and do not appear to contain tumor.

The spleen weighs 220 gm. and shows chronic passive congestion.

The kidneys each weigh 110 gm. and show passive congestion and arteriosclerotic changes.

The adrenals and bladder are normal.

Only the stump of the cervix uteri remains. (The patient had been operated upon for fibroids.) A red pedunculated polyp, 2 x 5 cm. is attached to the mid portion of the cervical mucosa and is bathed in a reddish mucoid secretion.

The aorta shows moderate arteriosclerosis.

The inferior vena cava contains no thrombi.

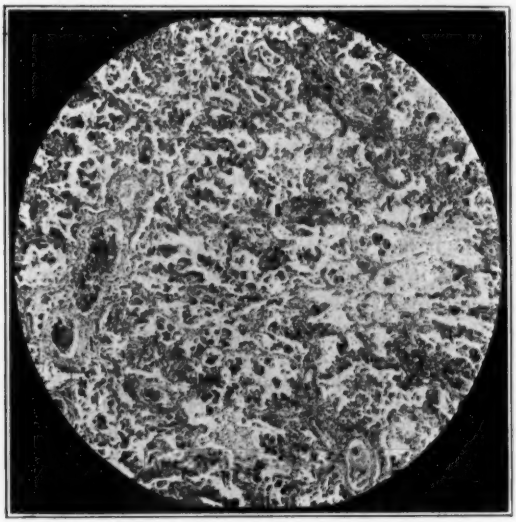

FIG. 1.—Case II. Cholangioma. × 70.

Microscopical Examination. Liver: Thirty sections are stained with methylene blue-eosin with phosphotungstic acid-hematoxylin and with Mallory's anilin blue. They show tumor consisting of cylindrical or cuboidal cells with a narrow basic stained cytoplasm and a large finely granular nucleus resembling very much that of the bile ducts. The tendency of the cells is to arrange themselves in acini which vary markedly in size. Some of the acini have a small lumen filled with necrotic material, some others have their lumen filled with tumor cells. The stroma of the tumor varies markedly in different parts, from a dense fibrous tissue containing a few tumor cells to delicate strands supporting single rows and large columns of epithelial cells (Fig. 1).

In the portal areas there is a proliferation of fibrous tissue and bile ducts. Many of the latter have their epithelial lining several

layers thick, partially occluding the lumen, while in others the epithelial cells rupture the basement membrane and invade the surrounding tissue.

There is a pressure atrophy of many of the liver cells as a result of tumor invasion and marked congestion of the sinusoids. Isolated liver cells frequently appear necrotic. There are also foci of necrosis, most marked about the central areas with many "polys" in the adjacent sinusoids attracted, no doubt, by the necrotic liver cells. Liver cells show tremendous fatty infiltration. Two sections show no tumor but considerable fatty infiltration.

Lungs: The tumor in the lungs resembles the primary tumor. The sections show nests of epithelial cells surrounded by a connective tissue stroma and like the acini are lined by epithelial cells several layers in thickness. The structure is typical of an adenocarcinoma. The lung metastasis is more cellular than the primary tumor and has invaded alveoli in which masses of tumor cells are found. Mitotic figures are present.

The remaining portions of sections show congestion of the alveolar capillaries. Large numbers of desquamated epithelial cells and a few polymorphonuclear leukocytes and endothelial cells are seen in the alveoli. A few of these contain plugs of fibrin and invading fibroblasts. Sections from trachea and attached lymph nodes show no tumor.

Lymph Node (Bronchial): It is surrounded by a thick capsule and contains abundant coal pigment. The central portion shows an extensive invasion of tumor cells. The cells and their arrangement are similar to the tumor elsewhere.

Heart: The heart shows chronic fibrous myocarditis.

Spleen and Kidneys: Sections from these organs show a chronic passive congestion.

Pancreas: There is an acute hemorrhagic necrosis, probably agonal.

Bladder: An acute cystitis is present.

Aorta: A moderate amount of arteriosclerosis is present.

Inferior Vena Cava: No tumor is found.

Microscopical Diagnosis. Adenocarcinoma of liver (primary) with metastases to lung, pleura and bronchial lymph nodes. Pleural effusion. Acute hemorrhagic pancreatic necrosis. Chronic fibrous myocarditis. Cervical polyp. Diverticulum of bladder. Absence of uterus, tubes, ovaries and appendix (operative).

CASE III.—A. L., female, aged sixty-six and a half years. This case lacks a clinical history. The clinical diagnosis as given in the autopsy protocol is "Carcinoma of the liver." Autopsy (H–11–945) performed by Dr. E. E. Tyzzer. Twenty-four hours postmortem. The body is considerably emaciated, 155 cm. long, and postmortem lividity is present.

The pleural cavities contain no fluid and no adhesions.

The lungs are light and all portions contain air. The left apex shows a puckered scar-like area 2 by 3 cm. On palpation, numerous small nodules are felt which measure from 1 to 10 mm. A few of these are in contact with the pleura. On section, they are finely subdivided, the subdivision being of a uniform size and measuring not over 0.4 mm. in diameter. They are pale pink and of a firm consistency.

From the abdomen about 2 liters of cloudy, rather thick fluid has been drawn off by the embalmer. This fluid clotted spontaneously into a firm mass. At the present time, the peritoneal cavity contains a small amount of fluid with flecks and small masses of fibrinous purulent exudate. There is a mass of exudate upon the superior surface of the liver near the anterior border. There is also a collection of grayish, shiny exudate with masses of clotted fibrin in the region of the cecum. There is no demonstrable appendix, but this organ is represented by a thin, ragged membrane measuring 5 cm. in length. Adjacent to this in the wall of the cecum is a small pocket of pus about 7 cm. in diameter. The cecum is small, contracted and has a rigid tough wall. The mesenteric lymph nodes are not notably enlarged.

The spleen shows passive congestion.

The stomach is markedly dilated, with a capacity somewhat over 3 quarts. The mucous membrane is normal.

The small and large intestines appear normal.

The pancreas appears normal throughout. Lying against the head of the pancreas, occupying the space between this and the liver, are several nodules of tumor tissue, the largest of which measures 3 cm. The tumor does not appear to have arisen in the pancreas.

The liver weighs 3800 gm. and extends 3 cm. below the costal margin. The liver tissue is replaced to a large extent by tumor tissue. There are a few smaller nodules but the tumor forms a more or less continuous mass extending throughout the entire organ. The interior of the tumor is necrotic everywhere, and of caseous consistency, opaque and yellowish in color. The peripheral portions of the liver are about equally involved.

The gall-bladder is filled with dark fluid slightly viscid bile in which are no calculi. The mucous membrane of this, as well as that of the duct, appears normal.

Both kidneys weigh 250 gm. The capsule strips readily, leaving a somewhat roughened, granular surface. The cortex measures 4 to 10 mm. and appears slightly opaque and of a brownish color.

The adrenals are normal.

The uterus is small and markedly atrophied. There are two small pedunculated tumors measuring 7 mm. on the peritoneal surface. The ovaries are senile. No tumor is present here.

The aorta shows many numerous areas of arteriosclerosis.

Microscopical Examination. Liver: The tumor in the liver is composed of epithelial cells having a tall cylindrical shape. The cytoplasm of the cells is clear and narrow and the nucleus vesicular, large, oval or round. The cells are arranged in a duct-like manner, the nuclei of which are pushed toward the periphery, and the small lumen filled with débris and necrotic material. In general, the cells and their arrangement resemble closely the bile ducts. Mitotic figures are present. The tumor is supported by a connective-tissue stroma which is more marked around the portal areas where it is fibrous. In the portal areas, the bile ducts seem to be increased in number and their lining epithelium is hyperplastic. There is also a marked lymphocytic infiltration. In some ducts the epithelium is desquamated and lies free in the lumen. There is much necrosis in the tumor. The liver substance surrounding the tumor is compressed and atrophic. The liver cells are also damaged in the parts remote from the tumor. The sinusoids are distended and filled with serum, blood and round cells.

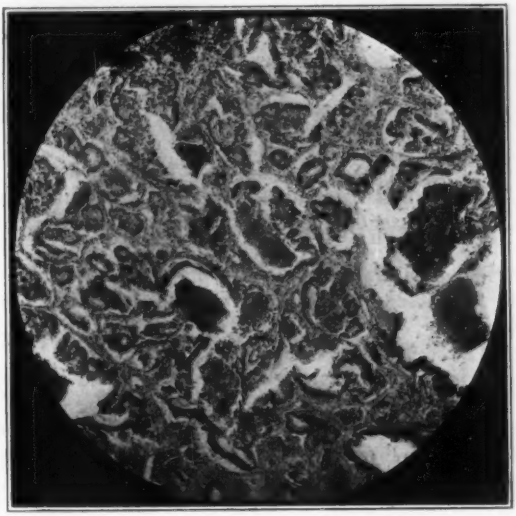

FIG. 2.—Case III. Cholangioma. Metastatic tumor in the lungs. × 70.

Lungs: In one section the tumor is situated beneath the pleura and shows a striking similarity by the type of cells, and their arrangement to the primary tumor and consequently to the bile ducts. In the center, the lung markings are destroyed, and the fibrous stroma dominates the picture. At the periphery the tumor plugs the alveoli, the outline of which is still recognizable. The lumen of the acini here contains necrotic material (Fig. 2).

In another section taken from the center of the lung, the tumor acini have no lumen and are closely packed together being supported by a delicate connective-tissue stroma. At the periphery, here also the tumor fills the alveoli, the walls of which can be made out. The parts of the lung free from tumor show marked congestion of the capillaries of the alveolar wall, but otherwise are not remarkable. The bronchi are normal.

The spleen shows marked passive congestion.

Microscopical Diagnosis. Carcinoma of liver, metastatic to lungs. Chronic and acute appendicitis. General peritonitis. Slight chronic pleuritis. Arteriosclerosis. Slight chronic nephritis.

CASE IV.—CLINICAL HISTORY. M. H., female, single, a housekeeper, aged sixty-two years, entered the Peter Bent Brigham Hospital complaining of jaundice.

Family History. Not remarkable.

Past History. Forty years ago she underwent an operation on the uterus or ovaries followed by an artificial menopause.

Present Illness. She has always had good health until seven weeks ago, when she began to feel wretched, had fever and chills, and went to bed. The local doctor diagnosed "jaundice." She noticed her urine was highly colored and also noticed her stools were of a grayish color.

Physical Examination. An obese woman with slightly jaundiced scleræ, coarse rales at bases of lungs posteriorly, and a loud systolic murmur over the apex and at the base of the heart. A systolic thrill is felt over the aortic area. The cardiac rhythm is irregular. The abdomen is distended, and the liver enlarged, extending below the umbilicus.

The patient died after five days in the hospital.

Clinical Diagnosis. Malignancy of liver; auricular fibrillation; mitral stenosis.

Autopsy (A–23–72) was performed by Dr. Wilens.

The body is that of a fairly well-developed and well-nourished white female, measuring 152 cm. in length. The entire body is tinted a yellow color and the scleræ are markedly jaundiced.

In the peritoneal cavity are many strong fibrous adhesions, attaching together several coils of both small and large intestine to the parietal peritoneum.

In the pleural cavity the right lung is entirely bound down by old fibrous adhesions and is firmly attached to the right side of the pericardium. The left pleural cavity is normal.

The heart is normal.

The right lung weighs 600 gm. and after removal is still covered with the parietal pleura. The lung tissue stands out quite firmly in places, suggesting bronchopneumonia. In the middle lobe, on section, a white opaque nodule is seen which measures about 1 cm.

in diameter. It is definitely firm and suggests a metastatic growth. The left lung weighs 400 gm. and appears normal.

The liver weighs 3680 gm. It measures anteroposteriorly 27 cm., transversely 26 cm. and vertically 20 cm. The margins are round and the surface smooth, shiny and greenish. Throughout the skin capsule innumerable grayish nodules from 0.5 to 1 cm. in diameter are seen. A large grayish mass, consisting apparently of several small nodules, is present in the lower right quadrant. Except for this area where the liver is very firm, the organ is soft and has a rather spongy feeling. On examining the large vessels *in situ*, no tumor is discovered within them (Fig. 3).

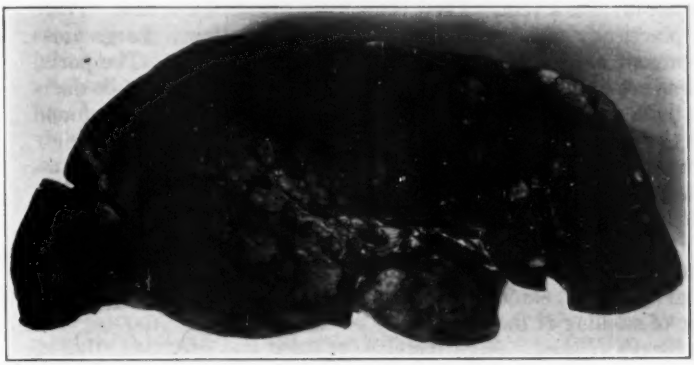

FIG. 3.—Case IV. Cholangioma. Note also the foamy appearance of the liver due to Bacillus welchii.

On section, a tumor mass measuring 5 x 6 x 7 cm. is found situated in the lower right quadrant of the liver. The outline of the tumor is irregular and at the periphery it seems to be composed of several small nodules, while in the center it is uniformly gray and contains a mass of necrotic material.

The liver was cut in slices 1 to 1.5 cm. thick. The cut section showed tumor nodules 0.5 to 1 cm. in diameter to be scattered practically all over the organ. The tissue between the nodules is bile stained and has a typical foamy appearance due to the invasion of the body by gas bacillus (B. welchii).

On dissecting the vessels grayish pin-point elevations—apparently tumor—are seen in various places. In no instance are the smaller or larger vessels found to be plugged or to contain tumor masses of a considerable size.

The gall-bladder is definitely distended to the size of a pear and on opening it, three large stones measuring 2½ cm. in diameter each are seen. The wall is markedly thickened but not inflamed. No ulceration or scars are found in the mucosa. Many smaller stones

are bathed in a thick mucous fluid. All of the stones are definitely black. The ducts are patent.

The heart weighs 320 gm. and is not remarkable.

The kidneys are normal.

The aorta shows arteriosclerosis of the ordinary type.

Microscopical Examination. Liver: Sections are taken from large and small nodules. The histology of various parts of the tumor is quite similar. The tumor cells both in appearance and arrangement closely resemble those of bile ducts. The cells are cylindrical or polygonal with a clear cytoplasm, and a round or oval vesicular nucleus, and a very deeply stained nucleolus. These cells are supported by a delicate connective-tissue stroma. In one section, the tumor invades a vein. There is much necrosis in the tumor. There is practically no normal liver tissue in the sections. Large areas represent either débris or extremely vacuolated cells. The portal areas are made out among the degenerated cells and the bile ducts in these areas are hyperplastic. A great many B. welchii are found in the sections.

Microscopical Diagnosis. Primary carcinoma of liver with metastases to right lung; arteriosclerosis; cholelithiasis; jaundice; fibrous pleurisy.

CASE V.—R. M., a German construction engineer, aged sixty-four years, married, entered the Peter Bent Brigham Hospital complaining of swelling of the abdomen.

Family History. Negative.

Past History. Heavy alcoholic addict in the past. Gonorrhea forty years ago. Syphilis thirty-eight years ago. Pneumonia twenty-eight years ago with complete recovery. Typhoid three years ago with complete recovery. Ten and a half years ago he had for about one year jaundice with clay-colored stools, and slight edema of the legs. During the past year, frequent epistaxis.

Present Illness. During the past year he has had attacks of progressive dyspnea on moderate exertion, and also attacks of palpitation, not associated with pain or dyspnea. Two months ago he vomited about one quart of blood and passed tarry stools. One week later (seven weeks ago), the abdomen and ankles began to swell, decreased for a time, but increased again about two weeks ago, with dull, constant pain in the lower abdomen. For two months his appetite has been poor, bowels very constipated and he has had excessive thirst and nocturia (2 to 3 times nightly).

Physical Examination. The patient is well nourished and well developed, with slight dyspnea and cyanosis and yellowish skin. The respirations are costo-abdominal in type. There is dulness and diminished tactile and vocal fremitus at both bases. Heart not remarkable. The systolic blood-pressure is 148, the diastolic 68. The abdomen is much distended, the abdominal wall markedly

edematous. The superficial abdominal veins are prominent and a fluid wave is present. There are no masses or tender areas. The upper border of the liver dulness is at the lower border of the fourth rib. There is edema of legs and thighs.

The patient was tapped twice and 15½ liters of yellow opalescent fluid was obtained in a period of six days. He was discharged and was readmitted ten days later. On tapping again, 10 liters of fluid were obtained of the same character as previously described. He was again discharged and readmitted eighteen days later. Eleven and a half liters of chyliform like, turbid fluid was removed. He died on the twelfth day of the last admission.

Autopsy (A–22–103): The autopsy was performed by Dr. B. Reifenstein, nineteen hours postmortem.

The body is that of an exceedingly well-developed and well-nourished adult, white male, measuring 165 cm. in length. There is slight edema of the lower extremities and some slight jaundice of the face and neck. The scleræ are icteric. The abdomen is full, especially in the flanks and gives evidence of fluid. In the midline below the umbilicus are several small scars of previous paracenteses.

The peritoneal cavity contains about 2500 cc of clear straw colored fluid. There are no adhesions. The mesenteric lymph nodes are not enlarged. The peritoneum is grayish in color, smooth and glistening. The diaphragm extends to the fifth rib on both the right and left sides. The appendix is somewhat fibrous in character, and extends downward over the brim of the pelvis. The spleen is slightly enlarged, and there are a few adhesions to the diaphragm. The liver is atrophic, nodular and does not extend to the costal margin. The gall-bladder is distended with bile. The small and large intestines are negative to external examination. The bladder is distended with urine. The vein of the round ligament is markedly dilated and filled with blood clot.

The pleural cavities contain no free fluid. The left lung is free from adhesions. The right lung is markedly adherent to the pleura over practically all the surfaces of the lung. Palpation of both lungs reveals numerous hard, firm, nodules, some on the surface and some located deeper in the lung tissue. Both lungs appear voluminous.

The mediastinum and pericardial cavity are not remarkable.

The heart weighs 350 gm. The mitral valve is markedly thickened and has calcareous deposits 2 to 3 mm. in diameter along the margins of the cusps. The aortic valve and portions of the arch also show rather marked arteriosclerotic thickening.

The lungs weigh (right) 705 gm. and (left) 725 gm. Both lungs are crepitant throughout and vary from a grayish-white color on the anterior surfaces to a reddish discoloration in the dependent parts. The pleura of the right lung is rough and denuded, due to its difficult removal on account of rather firm adhesions. Palpation

of both lungs reveals scattered, firm discrete areas from 1 to 8 mm. in diameter. These firm areas are especially more numerous along the anterior borders of the lungs. They are irregular spherical in shape, while in certain places conglomerations are formed. On section, these areas are brownish-yellow in color, resembling liver tissue, are elevated from the cut surface, and appear to be rather sharply outlined from the surrounding normal lung tissue. Some of these areas are firm and hard, while others appear softer, almost puriform in nature. On dissection of the smaller arteries of both lungs, small grayish-pink thrombi are found. Some of these are adherent to the vessel wall. Smears show them to be made up of some epithelial cells and a few cocci in pairs. The bronchi are negative. Some of the bronchial lymph nodes are enlarged up to a diameter of 1 to 2 cm. On section, these are rather firm and show some pigmentation together with several small brownish areas which may be tumor metastases. Some of the tissue surrounding the tumor nodules appears firm and red in color, as if there is a beginning infectious process.

The spleen weighs 280 gm. The markings are distinct and there is no evidence of tumor.

The gastro-intestinal tract and pancreas are normal.

The liver weighs 1320 gm. The organ and its surrounding structures are examined *in situ*. The most impressive thing is the symmetrical decrease in the size of the liver, all portions being involved. The surface is roughly nodular and pale brown in color. The nodules vary from 0.2 to 0.5 cm. in diameter, and project from the surface. The liver is hard and stiff, shrunken and deformed. The surface is roughened all over by projecting nodules of a yellowish-brown color. The shrunken tissue between the nodules is gray and translucent. On the surface are seen several larger nodular areas, slightly red in appearance.

Inspection of the inferior surface of the liver reveals the dilated vein of the round ligament and also shows the portal vein to be markedly enlarged and somewhat firm in consistency. Palpation of the gall-bladder reveals gall stones. The cystic and hepatic ducts are dissected out and found to be patent throughout. The portal vein reveals a most remarkable picture. In places the entire lumen is filled with a reddish-gray, rather soft, friable, almost puriform material which is somewhat adherent to the intima. Where it is adherent to the intima, there is a marked thickening of the wall of the vein. Most of this material lies free in the vein. The portal vein is dissected down to the splenic tributary. The thrombus apparently extends to this point and cannot be traced into the splenic vein. The vein of the round ligament is next opened and found to contain the same material. The para-umbilical vein between this vein and the portal vein is markedly dilated and filled with the same thrombotic material. The portal vein is dissected

into the liver, and here it is filled with a yellowish-red, soft material resembling tumor tissue. The hepatic veins are opened above, and contain some of the same necrotic tumor thrombi.

On section (Fig. 4) the liver has a mosaic appearance of nodular masses 2 to 6 cm. in diameter, separated by a somewhat retracted, grayish-white tissue. However, in areas and especially in cut surfaces of the larger nodular masses noted on the surface, there are found irregular, spherical, reddish-brown and yellowish-brown, adenomatous areas resembling normal liver tissue. Some of these areas are rather soft, and a smear taken shows them to be practically all epithelial cells. There are multiple nodules scattered throughout the liver. Frozen section from one of these areas reveals carcinoma of the liver. The esophageal veins are dissected out, but present nothing unusual. The spermatic vein is found and is rather dilated, perhaps due to collateral circulation.

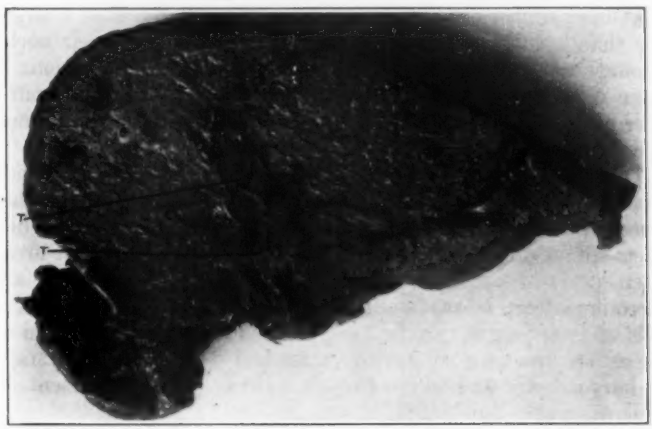

FIG. 4.—Case V. Hepatoma. *T*, tumor plugging the larger vessels.

The gall-bladder contains 10 stones about 1 cm. in diameter, each greenish in color and rather firm. The gall-bladder is not thickened. There are no scars or ulcerations in the mucosa.

The kidneys and adrenals show nothing remarkable.

The bladder contains bile-stained urine.

The prostate shows no evidence of tumor invasion.

The aorta is markedly involved by arteriosclerosis. There are numerous yellowish plaques, calcified areas, and several atheromatous ulcers.

The bone-marrow (femur) is composed of equal parts of red and yellow soft tissue rather characteristic of a secondary anemia.

Microscopical Examination. Liver: Sections are taken from tissue apparently free from tumor, and consisting only of sclerosed

liver substance, and also from tumor nodules. This is stained with methylene blue-eosin, Mallory's anilin-blue, phosphotungstic acid-hemotoxylin and by Pedrou's silver-nitrate method. The usual lobular arrangement in this section has been destroyed and instead there are isolated masses of liver tissue of a different size and shape, surrounded by large bands of connective tissue which are infiltrated with small round cells. The columns of liver cells in these areas have no longer their usual radial arrangement toward the efferent vein, which in some nodules cannot be found at all and in others is situated near the periphery. The liver cells in these adenomatous areas are of a normal polygonal shape, with one round nucleus and a deeply stained nucleolus. The cytoplasm of the cells has an excessive granulation and a somewhat "foamy" appearance. The nuclei are pyknotic in areas. The sinusoids in these areas are dilated, but contain very little blood. Many of the cells contain bile pigments.

At the periphery of some of these nodules, liver cells of a larger size than usual, with a pale cytoplasm, containing in their nuclei a somewhat increased amount of chromatin are seen. Occasionally these cells are in mitosis and are apparently newly regenerated liver cells. In some areas small liver nodules consisting of normal liver cells are present.

The portal areas contain an increased number of bile ducts which occasionally have their normal rosette appearance, and in other places are enlarged and have a cleft-like lumen. Some of the bile ducts sprout into the lobules. The fibrous tissue from these areas often penetrates the adenomatous nodules. Some lobules are necrotic and can be made out only by the presence of a few liver cells at their periphery. In many other lobules the cytoplasm of the cells represents a homogenous mass, and the nucleus is in a stage of karyorrhexis and chromatolysis. Hemosiderin is present in large masses.

Tumor: Tumor replaces entire lobules in very few instances. Parts of lobules are constantly present. The cells of the tumor resemble closely liver cells, being, however, of a somewhat smaller size. Their cytoplasm stained in blue is finely granular and their nuclei are round or slightly irregular, containing a nucleolus, rich in chromatin. The cells are arranged in tubules and in strands. The tubules are of a small size and each consists of one row of cells (Fig. 5). In most of them, a lumen is present containing a drop of bile (Fig. 6). The columns of tumor cells are mostly present at the periphery of the tumor nodules, and in few areas they are in a continuity with normal liver trabeculæ. This is conspicuous even under the low power where the difference in color of the cells is remarkable. Under the high power and especially with the oil immersion, the continuation of the liver cells into tumor cells is beyond any doubt. The tumor cells in these areas do not differ

markedly in size from the normal liver cells, the continuation of which they are. The difference is rather confined to the nuclei

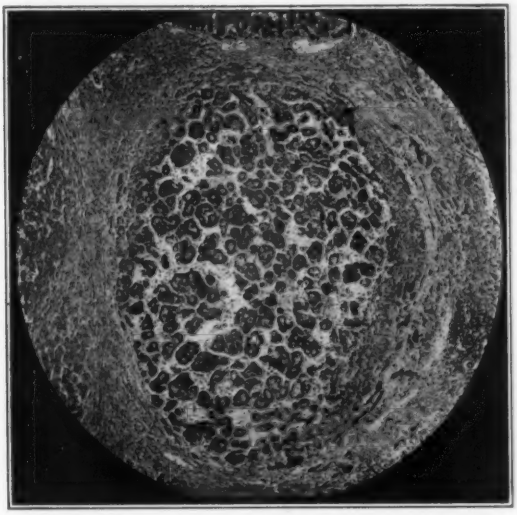

FIG. 5.—Case V. Hepatoma. A tumor nodule. × 70.

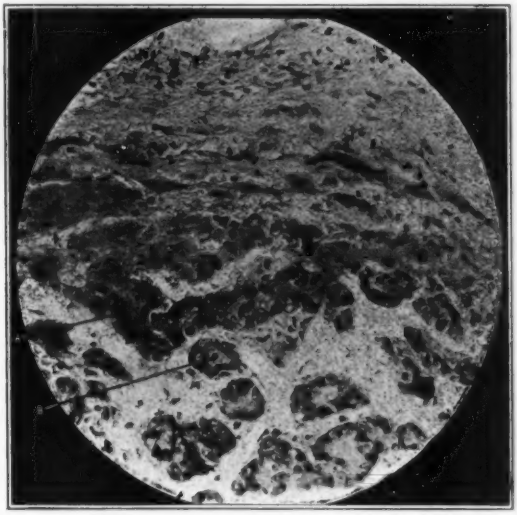

FIG. 6.—Case V. Hepatoma. *A*, continuation of normal liver cells into tumor cells; *B*, a drop of bile in the lumen of a tumor acinus. × 300.

which are larger and richer in chromatin. The cytoplasm is stained with basic stains instead of the usual acid (Fig. 6). Mitotic figures could not be found in the sections.

Vessels: The vessels are largely invaded by tumor (Fig. 4). The portal veins in some areas are markedly distended, in others are of normal size and plugged with tumor. This is conspicuous not only in places where the tumor dominates the picture, but also in tissue very slightly touched by new growth.

Stroma: The stroma of the tumor consists of fine capillaries and closely resembles liver stroma (Fig. 7). No connective tissue is found between the tumor cells and group of cells.

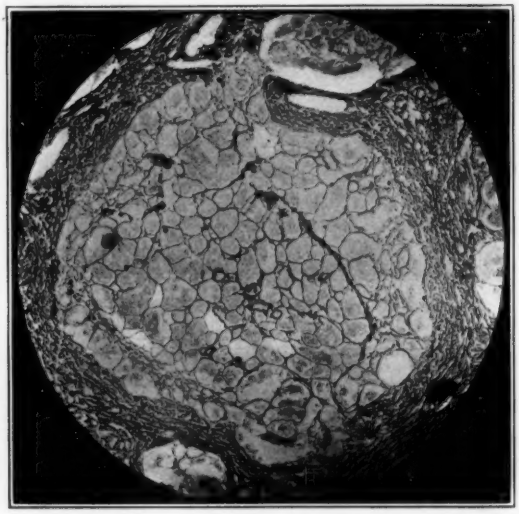

FIG. 7.—Case V. Hepatoma. The capillary stroma of the tumor. × circa 55.

Lung Metastases: The tumor cells here are strikingly similar to those of the liver in their size, shape and staining properties. *These cells also secrete bile.* They are arranged in acini and irregular cords of columns with intervening sinusoids, so typical of the liver structure (Fig. 8). The tumor nodules are sharply demarcated from the lung tissue, the alveoli of which in the adjacent parts are collapsed and in the remote areas normal. Tumor tissue is found in the pulmonary vessels and in the perivascular lymphatics which are dilated. The stroma of the tumor here is also similar to the tumor stroma of the liver, being composed only of capillaries.

Spleen: Weighs 280 gm. and shows passive congestion.

Pancreas: Normal.

Kidneys: Arteriosclerotic changes in the vessels.

Adrenals: Normal.

Aorta: Atheromatous changes of the ordinary type.

Microscopical Diagnosis. Primary carcinoma (hepatoma) of the liver with metastases to the lungs. Tumor thrombi in portal and hepatic veins. Cirrhosis (portal) of the liver. Cholelithiasis. Ascites. Icterus. Chronic pleuritis (right). Arteriosclerosis; hypertrophy of prostate.

Discussion. As can be seen from the descriptions, the first 4 cases have in common:

1. The type of cells which closely resemble those of the smaller bile ducts, cuboidal or cylindrical cells with a narrow or large cytoplasm, a large vesicular nucleus and a deeply stained nucleolus.
2. The duct-like arrangement.
3. The connective-tissue stroma.

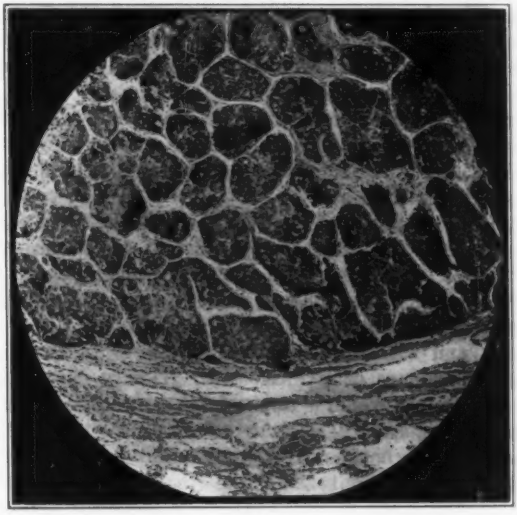

FIG. 8.—Case V. Hepatoma. Metastatic tumor in the lungs. × 70.

In the fifth case the tumor cells are polygonal with a large, granular cytoplasm, containing a deeply stained nucleus. The cells resemble closely liver cells, not only morphologically, but also by their property, in the main tumor as well as in the lung metastases, of forming bile. The stroma in the tumor is also similar to the stroma of normal liver.

At one time there was a good deal of discussion as to whether the type of tumor was a hepatoma or a cholangioma, and the criteria for the differentiation between the two were based on the property of imitation of the structure of the tissues from which

they arose and the resemblance of the tumor cells to the matrix type cells.

However, cases were reported in which benign liver-cell adenoma had given rise to a duct-like structure (Orth quoted by Goldzieher and Bokay). It was also shown that the cells of the two varieties of tumor (hepatoma and cholangioma) may closely resemble each other. According to Ewing,[11] "Some cases are so far removed from their usual morphology that some doubt must always remain regarding their true origin."

Wegelin[14] and Yamagiwa[7] reached the conclusion that the stroma is a reliable criterion in the differentiation between the two types of tumor.

In hepatoma, the stroma consists of capillaries par excellence, while that of cholangioma is never composed only of capillaries.

The relation of liver cells to the capillaries, says Yamagiwa, quoted by Winternitz, is a property preserved by the tumor for the longest time, and apparently the tumor has the power to stimulate the endothelium of the vessels in which they lodge, to the formation of new capillaries of the liver nodule.

By using Pedrou's modification of Bielchowsky's silver-nitrate method we were able to demonstrate the striking similarity of the stroma in the normal liver tissue to those of the tumor in the liver and in the lungs (Fig. 7).

Thus, the resemblance of the cells of the tumor to the matrix type cell, the property to imitate the structure of the tissue from which they arise, and finally the stroma leads us to classify Cases I, II, III and IV as bile-duct carcinoma or cholangiomas, and the fifth case as a liver cell carcinoma or hepatoma.

Cirrhosis and Primary Carcinoma of the Liver. The strikingly frequent coincidence of cirrhosis with primary carcinoma of the liver, a coincidence which is unusual when the liver is the seat of a metastatic carcinoma, has impressed observers with the probable etiological relation between the two conditions.

The following tables taken from Winternitz, to which I have added statistics given by other observers, illustrate the percentage of the coincidence of primary carcinoma with cirrhosis.

HEPATOMA.

	Number of cases.	Percentage with cirrhosis.	Percentage without cirrhosis.
Eggel	60	86.4	13.60
Golzieher and Bokay	14	100.0	0.00
Yamagiwa	27	74.75	25.25
Karsner[12]	4	100.0	0.00
Winternitz	6	100.0	0.00
Pirie[13]	28	100.0	0.00

CHOLANGIOMA.

Eggel	8	62.5	37.50
Goldzieher and Bokay	7	42.8	57.20
Yamagina	15	46.7	53.30

The combined statistics, however, demonstrate that hepatoma is associated with cirrhosis in about 87 per cent of cases, and cholangioma is about 51 per cent.

Wegelin[14] advanced the conception that cirrhosis follows cancer, explaining that as a result of the new growth, the liver parenchyma undergoes atrophy and necrosis, thus giving rise to the formation of scar tissue. However, the opinions that carcinoma follows cirrhosis is prevalent among pathologists.

Cirrhosis is explained as a repair process, due to injury followed by a compensatory hypertrophy and hyperplasia of the liver cells giving rise to the formation of multiple adenomatous nodules which may eventually become excessive to such a degree as to form carcinomata.

In a recent study on the incidence of hepatic carcinoma in the natives of Africa, Pirie[13] found that primary carcinoma of the liver is much more frequent among natives than among Europeans. Thus in 96 cases diagnosed as carcinoma during a period of nine years (1912–1921) 36 were found to be primary in the liver. Twenty-eight of the 36 were liver-cell carcinoma, 3 bile duct, and 5 of a doubtful or mixed origin. *Cirrhosis was present in all of the 28 liver-cell carcinoma.* In searching for an explanation of the striking frequency of primary liver carcinoma and its association with cirrhosis in the natives, Pirie believed the cause to be schistosomiasis. The presence of the latter was definitely established by the author in 10 of the 36 cases, while in 24 information was lacking and only in 2 cases could it be excluded.

Schistosomiasis, as pointed out by Pirie, has been shown experimentally to induce cirrhosis of the liver. Fairley produced experimentally a bilharzial (S. hematobium) cirrhosis in monkeys. It is rather of interest to note that he believes the cirrhosis to be due not to the presence of the ova alone, which are present in a very scant number in the liver, but also to the bilharzial toxin present in the blood stream and which is filtered out in the liver. Fisher regards the deposit of the eggs of S. japonicum as the cause of the majority of the cases of cirrhosis of the liver in China. Symmers described a gross form of cirrhosis, "pipe-stem" cirrhosis, associated with the deposit of large numbers of bilharzial ova in the liver. (All the above mentioned authors are quoted by Pirie.) As a result, Pirie concludes: "Schistosomiasis may be a factor in accounting for the common occurrence of carcinoma of the liver among South African natives, through leading first to the development of cirrhosis on top of which a carcinoma may develop."

In the cases I, II, III and IV (cholangiomas) here reported, we believe the fibrosis to be secondary to the tumor, while in case VI (hepatoma) the tumor undoubtedly occurred on top of a previously existing portal cirrhosis.

Is the Tumor Multicentric or Unicentric in Origin? The multi-

centric origin of carcinoma of the skin, stomach and intestines was reported by different authors (Krompecher,[15] Peterson, [16] Versé,[17] Hauser,[18] Ménétrier, [19] and others).

Recently, Dr. Margaret Warwick,[20] at a meeting of the Association of Pathologists and Bacteriologists in Boston, in an interesting demonstration, produced evidence of the multicentric origin of squamous cell carcinoma of the lower lip.

Siegenback van Heukelom,[21] was the first to advocate the multicentric origin of primary carcinoma of the liver, basing his opinion on the observation of the transformation at the periphery of the tumor nodule of normal liver cells into cancer cells. He describes, for instance, columns of tumor cells as the continuation of normal liver cells and tumor capillaries in direct continuation with normal liver capillaries.

Goldzieher and Bokay[6] also describe such transformation in some of their cases (10, 15 and 20) and believe in multicentricity.

Adelheim,[22] in a study of 1 case of hepatoma without metastases to the lung or other organs, following nodular cirrhosis, demonstrates the "transformation" and convincingly advocates the multicentric origin of the tumor in his case.

Yamagiwa,[7] on the ground that primary carcinoma of liver arises either as a regenerating hyperplasia of liver cells or as inflammatory hyperplasia of bile ducts, emphasizes the probability of multicentricity of every primary cancer of the liver.

The idea of appositional growth is energetically denied by Ribbert,[5] who affirms that "Der völlig entwickelte Krebs wächst immer nur aus sich heraus" and by Borst (quoted by Ménétrier) who affirms that "the carcinoma on the border advances with its own troops and does not add to itself new soldiers at the expense of healthy tissue."

The fact that tumor thrombi are found practically always in the liver vessels indicates once more, according to Ribbert, that the tumor spreads by the way of metastases to other organs and to other points in the liver itself.

Winternitz,[9] who is also against multicentricity, emphasizes the presence of tumor masses in the vessels of the portal areas.

Helvestine[23] reported 1 case of hepatoma *without cirrhosis* in which the cancer cells grew between parallel capillaries and were in direct continuation with the liver cells trabeculæ, but there was no transition between liver cells and tumor cells. He compared the case with a metastatic carcinoma from the gall-bladder and found appearances very similar to those found in the hepatoma, and as a result he concludes the growth to be unicentric.

To trace the multicentric origin in cholangioma is not always possible, because of the fact that the cases come to autopsy when the liver is markedly involved by the new growth and the large tumor

mass present might well be due to the confluence of several small nodules which had started at different points at the same time.

However, as has been pointed out in the description in cases I, II, and IV the tumor appears to be confined mostly to the portal areas from which it extends for some distance. Even beyond this extension, there is a marked proliferation of the bile ducts the cells of which, in places, are taller than normal and form papillary projections into the lumen. In Case II they rupture the basement membrane and invade the surrounding tissue.

These facts, in connection with the opinion expressed by Yamagiwa, that the tumor is due to an inflammatory hyperplasia of the bile ducts, are suggestive that the growth is multicentric.

As regards the hepatoma, two facts dominate the picture:

1. The strikingly diffuse and practically *uniform* distribution of the tumor corresponding to the involvement of the liver by the cirrhotic process, which suggests that the tumor started at different points at the same time.

2. The relative scantiness of tumor metastases in the lungs and the absence of metastases in other organs as compared with the extreme invasion of the vessels, rather plugging them by the new growth.

This "invasion" upon which so much stress has been laid to prove the unicentric (metastatic) theory, I believe (in the case reported here) to be due to a passive discharge of tumor mass into the vessels. This belief is strengthened by the fact that the tumor in the vessels is found to be largely necrotic. Dr. Wolbach (personal communication) observed a case where the tumor thrombus extended into the vena cava up to the heart.

The presence of tumor metastases in the lungs, however scant they are, obviously shows that the tumor spreads by metastases also.

Correlating the facts just mentioned with the "transitions" described by Heukelom, Goldzieher and Bokay and others and also found by myself in many areas in Case V, I am inclined toward the conception that the growth spreads in unicentric as well as multicentric manner believing that in hepatoma the latter is the principal way in the spread of the new growth.

Clinical. The first writers on the subject believed they were able to diagnose not only the disease but even the type of cancer (nodulary, massive and so forth). In time, however, this belief was disproved, and from the records reported in the literature, the diagnosis of primary carcinoma of the liver was rarely made antemortem. In most instances the clinical picture points rather to a cirrhosis or to any liver disturbance producing portal obstruction. Jaundice, edema of the lower extremities, ascites, weakness and loss of weight are the leitmotif of the patient's complaint.

The involvement of the lungs is, of course, not as rare as it is commonly taught, and occurs probably early. There are, however, few signs on physical examination, as is seen in Case II, where in spite of extensive metastases to both lungs the attention of the clinician was drawn to the *extensive* involvement of the lungs by the low vital capacity which was about 41 per cent of normal.

The difficulty in diagnosis is amply demonstrated by the fact that *in none of our cases* was the condition diagnosed antemortem.

AGE AND SEX. Primary carcinoma of the liver attacks people practically of the same age as carcinoma elsewhere, notably between the fourth and fifth decades. In our cases, the age varies between sixty-one and sixty-six years. However, many cases have been reported of primary carcinoma in children.

Hepatoma seems to be more frequent in males, while cholangioma in the female is prevalent. This may be explained by the predominance of cirrhosis of the liver in men, and bile-duct infection, followed by an inflammatory hyperplasia of bile ducts, in women.

COURSE. According to the literature, primary carcinoma of the liver runs a rapid course and is rarely of more than three months' duration.

In the cases here reported the exact onset of the disease was impossible to determine. The patient's attention to this condition is generally drawn two to three months before exitus.

Summary and Conclusions. Five cases of primary carcinoma of the liver are reported. Cases I to IV are classified in cholangiomas, or bile-duct carcinoma, and Case V is classified as hepatoma, or liver-cell carcinoma.

The differential diagnosis between the two varieties of tumor is based:

1. On the type of cells. In cholangioma, the cells resemble those of the smaller bile ducts; in hepatoma, the liver cells.

2. On the arrangement of the cells. In cholangioma they have an arrangement closely resembling bile ducts, while in hepatoma they are arranged in columns, imitating the normal liver structure.

3. On the type of stroma which is considered as the most reliable criterion. In cholangioma, the stroma is fibrous, while in hepatoma it consists of capillaries, strikingly resembling the normal liver stroma, not only in the liver tumor but also in the lung metastases. This is demonstrated by Pedrou's modification of Bielchowksy's silver-nitrate method.

In all 5 cases metastases are present in the lungs and in 1 case also in the kidney.

Tumor is found invading the liver vessels in all cases.

In the hepatoma (Case V) areas of transition between normal liver cells and tumor cells are present.

Both varieties of tumor are believed to spread by either way: multicentric and unicentric.

In hepatoma, the tumor has occurred on top of a cirrhosis, while in the cholangioma the fibrous stroma is secondary to the tumor.

The 4 cases of cholangioma here reported, happened all in women. The age of the patients varied between sixty-one and sixty-six years. The hepatoma happened in a man.

Ascites was present in 3 cholangiomas and also in the hepatoma.

The exact onset of the disease in the cases reported was impossible to determine, but the patients attention was drawn to this conditon two to three months before exitus.

In no instance was the diagnosis of this condition made in the cases reported antemortem.

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THE SURGERY OF PULMONARY TUBERCULOSIS.*

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(*Continued from July*, 1924)

Cavities whose walls are not very stiff are obliterated to mere clefts by successful thoracoplasty; these clefts then fill with granulation tissue rich in bloodvessels and become obliterated, or a smooth, clean mucous membrane replaces the previous dirty lining.

The uncompressed lung compensates for its compressed fellow by becoming huge with emphysema and hyperplasia.

Brauer does not think that in a resting patient any noteworthy greater functional demand is made upon the functioning lung, except perhaps during the period immediately following the operation, before it has accustomed itself to the sudden change in intrathoracic pressure conditions. Sauerbruch, on the other hand, states that the uncompressed lung, especially in the young, moves much more after operation, and that this causes a more rapid movement of lymph and, if it contains tubercle bacilli, dissemination of disease, and that the increased movement may be responsible for the breaking down of partially healed lesions. It is for these reasons that Sauerbruch lays such great stress upon the necessity of the better lung being absolutely free of tuberculous activity if the worse lung is to be permanently compressed by thoracoplasty.

IV. Thoracoplasty Compared with Artificial Pneumothorax. At present the working rule that thoracoplasty is never to be used when satisfactory artificial pneumothorax is obtainable is almost everywhere strictly observed. Inquiry into the differences between the methods, and the relation between them, will be of value for a better understanding of thoracoplasty.

The number of patients whose pulmonary disease is sufficiently unilateral to warrant compression of one lung is variously estimated at from 2 to 10 per cent. Matson *et al.* attempted artificial pneumothorax in 600 of 7000 patients, or 8.5 per cent; of these, 120 (20 per cent) had no free pleural space. In 248 (41.3 per cent) only partial compression was obtainable, and the clinical cures were only 15.5 per cent, whereas the satisfactory compressions produced 45 per cent of clinical cures. Saugmann has reported the results of attempted artificial pneumothorax upon 211 third-stage tuberculous patients: 70.2 per cent were able to do "ordinary light work" when the pneumothorax had been complete; 33.3 per cent when there were only limited adhesions; only 11.1 per cent when there were extensive adhesions, and 11.8 per cent when no pneumothorax at all was realizable. Saugmann estimated that he failed to produce satisfactory compression in 30 per cent of his attempts; von Muralt

gives 20 to 30 per cent as his figures; Brunner 50 per cent; Stuertz 20 per cent; Powell and Hartley 30 per cent. Thoracoplasty is not indicated, however, for all cases in which pneumothorax has failed (this will be discussed under indications and contraindications).

Madinier and Saugmann estimate that 4 to 8 per cent of their patients are suitable for surgical therapy. I believe that with conservative choice of cases, 2 per cent is nearer the true estimate for unselected groups of tuberculous patients.

Experience has taught that the only sure way of telling whether or not a pleural cavity is so far obliterated by adhesions as to prevent the production of an artificial pneumothorax is to try to find a free pleural space by repeated actual trials. In other words, the usual signs of adhesions are not sure clinical signs, as a much contracted chest may mean only an advanced pulmonary sclerosis with a free pleural cavity. However, a history of pleurisy, a sunken chest in a chronic ulcerative phthisis, diminished respiration and fremitus, and a negative Litten's sign, and an immobile diaphragm as determined by physical examination and roentgen-ray, are practically certain evidence of extensive pleural synthesis.

Numbers of series of cases show that the final results of pneumothorax and of thoracoplasty are about the same, that is, roughly, 35 per cent cured, 30 per cent improved, 35 per cent uninfluenced, worse or dead. Empirically, therefore, it cannot be claimed that thoracoplasty is less effective because it produces less compression than pneumothorax. Each method has certain advantages over the other that will be of interest to examine.

Pneumothorax, in contradistinction to thoracoplasty, is non-deforming, non-shocking, and as compression is produced gradually, at many sittings, it avoids the dangers of acute circulatory and respiratory upsets, and of pneumonia from aspiration of large amounts of expressed secretions, or failure to expectorate them on account of operative pain. Also, as accumulated toxins are only gradually squeezed out of the lung into the general circulation (auto-tuberculinization) there is little danger of lighting up tuberculous foci elsewhere in the body, and the operation of pneumothorax, *per se*, does not lower general resistance. Pneumothorax has the advantage that it may be rapidly released (provided it is not of long standing and the lung and pleura much fibrosed—for then attempted release only aggravates the dyspnea) in case pneumonia, pleurisy, severe bronchitis or progression of tuberculosis (7.3 per cent of Matson's 480 cases) develops in the opposite lung. Thoracoplasty once done is beyond recall, and the complications just named are liable to be fatal.

Although thoracoplasty upon tuberculous persons is distinctly a major operation with a definite operative mortality (2 to 10 per cent), the new technic, and especially operation in several stages, has made it remarkably safe. While the operation of artificial

pneumothorax is an essentially trivial procedure, it entails many grave risks. Gas embolus and "pleural eclampsia" are real dangers, although not always fatal. Forlanini had 4 such "accidents" among 1454 gas fills (0.27 per cent), or 14.28 per cent of the patients under treatment. Matson *et al.* had two fatal cases (0.33 per cent) of gas embolus; 2 fatal, and 15 non-fatal cases of "pleural eclampsia."

It is generally estimated that 50 per cent of all pneumothoraces develop serous effusions during the course of treatment. In many of these, fibrinous adhesions form under the fluid and slowly but certainly draw the lung out to the chest wall where it adheres tightly and obstinately refuses further gas compression. McKinnie estimates that 5 per cent of these effusions become purulent, a grave complication, especially if the pus becomes secondarily infected. Of Matson's 480 cases 12.3 per cent developed purulent effusions. When the pyo-pneumothorax occurs suddenly from a large rupture of the lung or of a superficial, thin-walled cavity (usually as the result of trying to stretch adhesions with high positive gas pressure) the outcome is most frequently early death. Of Sauerbruch's 73 cases of cavity rupture, 57 were caused by such attempts to stretch adhesions; of these 57, 43 died during the first week, 6 in later weeks, a total mortality of 86 per cent. Of his 16 spontaneous pneumothoraces only 4 died (25 per cent). Spontaneous pneumothorax occurred in 3.3 per cent of Matson's series.

It is common knowledge that the immediate results of pneumothorax are frequently so satisfactory to some patients that they fail to return for the necessary continuation of the treatment. Fishberg believes that most poor people abandon pneumothorax refills after leaving the sanitoria, and on this account advises the treatment only for the well-to-do who can, and will, continue. Once the gas has absorbed and the lung expanded, firm pleural adhesions form, and almost invariably prevent resumption of pneumothorax therapy when the wayward patients return for it because of the return of active symptoms; then thoracoplasty must be resorted to. Ten (2.08 per cent) of Matson's 480 patients abandoned treatment too soon because they were doing so well. According to the case, it is necessary to inject gas every two to three weeks for from one and a half to three or more years. In 1923 Gravensen, Saugmann's successor, wrote that he "usually maintains an optimal pneumothorax three to five years." There are many who loathe the prospect of being the object of even so minor an operation over a period of years. A thoracoplasty once done is done; and for this reason may be considered especially indicated for those poor or shiftless persons who might be expected to abandon pneumothorax treatment prematurely. As the improvement after the first stage of the operation is rarely so marked as to lead the patient to believe that he is cured, he almost invariably accepts the second and final stage. In regard to its permanancy, thoracoplasty possesses a far

more important advantage than this. In a typical case, after a long period of pneumothorax treatment, during which all the symptoms of tuberculosis have disappeared, the physician in charge decides to stop the gas injections and to allow the pneumothorax to absorb. This has been aptly described as "a jump into the dark," as it is always impossible to predict when tuberculosis is permanently healed. Arrest of the disease has been effected by pulmonary rest, and the encapsulation of tubercles and cavities with fibrous tissue, which by shrinking has made the lung relatively smaller than its containing chest wall. As such a lung expands, the encapsulating fibrous tissue is tugged at, and unless very firm it will be torn apart and the tubercles it contains exposed and activated, and cavities pulled open. This reactivation of the tuberculosis is not infrequently observed clinically, but often after pleural adhesions have formed, preventing resumption of gas compression; in such cases thoracoplasty becomes necessary. As the lung expands, it resumes respiratory movements—a further stimulus to reactivation of the disease. It is sometimes claimed that one of the most important advantages of pneumothorax over thoracoplasty is that after release of the gas the lung resumes its normal function instead of being forever useless. As a matter of fact, if the compressed lung was extensively diseased before the institution of the pneumothorax, it will become so filled with scar tissue after one or two years of treatment that it is of little use in respiration after it has expanded.

As the chest cavity is larger than the greatly shrunken lung that is expected to fill it, various changes occur in an attempt to compensate for the discrepancy: the hemithorax flattens and the ribs crowd together, and the heart and mediastinum and diaphragm shift toward the affected side and the relatively normal portions of both lungs become emphysematous. If these changes do not suffice, the intrapleural negative pressure becomes very great as the gas is absorbed, pain and dyspnea may be marked, and "transudates *ex vacuo*" appear. After many months these transudates may become purulent and require eventual thoracoplasty.

Within the past two or three years several clinics have been using phrenicotomy in conjunction with pneumothorax; the marked rise of the diaphragm has been found largely to compensate for the disproportion between the chest and contracted lung. This will be discussed further under the section, paralysis of diaphragm.

There are certain cases in which thoracoplasty would be chosen in preference to pneumothorax. It is preferable to the operation of intrapleural pneumolysis, or the use of Jacobaeus' thoracoscope and cautery for adhesions (except when they are few, long and slender) that are preventing a completely satisfactory gas compression. The combination of either of these operations with artificial pneumothorax exposes the patient to the dangers and later complications of two distinct operative procedures. Thoracoplasty is

also preferable to attempts to stretch or tear adhesions, which may be near superficial lesions or cavities, with high gas pressures, because of the danger of lung rupture and rapidly fatal empyema (Blanchette; Olbrecht; Sauerbruch—see his statistics above). Sometimes a gas compression will be satisfactory except for one adhesion located over a cavity, and which may pull in such a way as to cause hemorrhage. Such cases need thoracoplasty. There are certain stiff-walled cavities that thoracoplasty will collapse after pneumothorax has failed (Brauer; Læon Bérard).

Some surgeons with wide experience with both methods believe that thoracoplasty is preferable to pneumothorax, although few are as yet sufficiently firm in their belief to expose their patients to the dangers of a major operation, if satisfactory compression is obtainable with pneumothorax. Sauerbruch considers thoracoplasty more "bedeutungsvoll" than artificial pneumothorax, and says that many doctors, who are in the position to compare the results of the two methods, "recognize the better and lasting results of extensive rib resection." On the basis of a comparison of Jehn's 6 necropsies upon old thoracoplasty patients with necropsies upon pneumothorax patients, Sauerbruch says that the fibrous tissue is greater in amount after thoracoplasty than after pneumothorax.

Hauke points out the fact, which he admits may be more of theoretical than practical importance, that as the air of a pneumothorax is always absorbing the lung is continuously expanding, whereas after thoracoplasty the "deribbed" chest wall falls in, in proportion to the amount of pulmonary fibrosis, until rib regeneration finally fixes it. Bérard and Dumarest believe that pneumothorax bulges the mediastinum farther toward the better lung than does thoracoplasty, and, in demanding more strenuous work of it, exposes any latent lesions that it may contain to greater danger of activation. Jessen believes that thoracoplasty is indicated for all very severe lesions, because the lasting results are better, and says, "the results from thoracoplasty, if the indications are properly placed, are reached by no other method." When compression therapy is indicated, Trembley, an internist, would advise thoracoplasty in preference to pneumothorax (because of the many dangers, complications and uncertainties of release of the latter) if two-thirds of a lung were considerably diseased. Bérard and Dumarest use thoracoplasty (partial) in the presence of a free pleural cavity for localized, ulcerative infiltration or cavity of the base, and Moreau and Olbrechts would prefer a complete thoracoplasty for pneumonic types of infiltration which are little influenced by artificial pneumothorax. Stöcklin, an internist, thinks that better care in selecting cases and better technic will make thoracoplasty results surpass those of artificial pneumothorax, and adds, "it is, indeed, to be expected that in the future thoracoplasty will prove superior to pneumothorax."

V. Indications and Contraindications. Only through active coöperation between internist and surgeon is it possible to select cases rationally and to avoid great disappointments. In brief, surgical compression may be said to be indicated for largely unilateral lesions, when all other treatment, including a sufficiently long sanitorium régime and attempted artificial pneumothorax, has failed.

At present few internists will recommend operation until the patient has "cured" for many months and has steadily "lost ground," and for whom death seems a certainty. Operation is usually thought of only as a last refuge, and that it has been able to accomplish so much even in such cases is promise that it may be expected to accomplish much more when broader experience more clearly defines the exact indications and contraindications, and when patients are referred for surgery before the disease has become far advanced with cavity formation and, perhaps, repeated hemoptyses. Davies advises operation if there has been no improvement after six months of faithful sanitorium régime, but would operate at once if cavity exists. From many experienced surgeons and internists comes the plea for earlier operation, especially for patients with incomplete artificial pneumothoraces who are not making satisfactory improvement.

Contrary to expectation it has been found that even very sick tuberculous persons, with high fever, cavities and much sputum, stand these major operations remarkably well. However, both Sauerbruch and Schottmüller point out the danger of operating upon those who have demonstrated an abnormally poor resistance to tuberculosis, or whose family tuberculous history is markedly bad.

Age. In general the operation should be limited to patients between fifteen and forty-five years of age. However, apparent age, and the condition of the cardiovascular system are more important than actual age. Sauerbruch does not hesitate to perform the two-stage operation upon a person over fifty if the general condition is satisfactory, nor upon a child under fifteen, if lung compression is absolutely indicated. In children the bony tissues are so plastic that only very small resections are needed to obtain considerable compression. Jacobaeus and Key had definitely bad results among patients under twenty, and say this is also the experience of other surgeons. Brauer states that the indications for operation are the same in children as in adults, but that it should be advised for the young only with the greatest caution; the common caseous, hepatized forms, with hilus foci, not uncommon in children, are to be avoided. It is still too soon to know if the favorable results thus far obtained will outlast puberty. As there are not often many adhesions in children, pneumothorax is usually possible (Brauer); Eliasberg has reported good results with it in parenchymatous lesions, and says that without it children are sure to die.

The Worse Lung. Very extensive diseases of even three lobes of one lung is no contraindication, provided that the patient's general condition is satisfactory. A great majority of the reported cases had cavities, and the most startling immediate results have occurred in them. Operation is especially indicated where basal lesions are marked, as spontaneous healing is rare on account of the great range of respiratory movements (Saugmann; Madinier). Better results are obtained from operation upon the left lung than upon the right; this is said to be due to the facts that the compression of the left side is relatively greater because the left lung is smaller, and that relatively less work is thrown upon the right lung, it being larger. Of Schottmüller's 100 cases, 57 were operated upon the left side: there were 40.4 per cent final cures and 17.5 per cent final deaths; 43 were on the right: 32.5 per cent cures and 32.5 per cent deaths. Of Sauerbruch's last 116 operations 63 were left-sided: 52 per cent lost tubercle bacilli, 24 per cent improved, 10 per cent remained unchanged, and 14 per cent died; 53 were on the right: 20 per cent lost tubercle bacilli, 30 per cent improved, 12 per cent remained unchanged, and 36 per cent died. Of Bull's 75 operations, 46 were left-sided, and there were 2.2 per cent operative deaths; 29 were on the right side, with 26 per cent operative deaths. Of Jacobaeus and Key's "positive results" 18 were on the left side, 6 on the right; of their "negative results" 11 were on the left side, 7 on the right.

In regard to lung pathology it is of the greatest prognostic importance that the lesions be predominately chronic and fibrous, or "productive" in type, rather than rapidly progressive, caseous, or "exudative" in type, for these last do not respond so favorably to compression. Productive lesions are distinguishable by roentgen-ray and physical examination: the individual lesions are dense and compact, the chest is contracted, the heart, mediastinum and trachea pulled over and the diaphragm up, and the ribs are inclined markedly downward and are close together. The lesions among Sauerbruch's last reported 116 cases were predominately productive in 67, and months or years after operation there were only 10 per cent of deaths; among 49 predominantly exudative cases there were 43 per cent deaths. Progressive, exudative lesions in the worse lung usually imply progressive tuberculous activity in the better, and the results, therefore, are frequently bad. Patients with such lesions may be operated upon only as a last resort, and only then when their general condition is good, and when the "good lung" is free of even small "spots." Jacobaeus and Key had 7 unfavorable results from operation upon 7 patients whose tuberculous history dated back less than one year.

Sauerbruch does not consider great amounts of sputum a contraindication, provided the patient is an otherwise suitable case. He

has operated where there were 1000 cc a day, which became reduced to 1 or 2 cc a day.

Some form of surgical compression is indicated for recurrent severe hemoptyses when artificial pneumothorax cannot be produced, or where adhesions, in the presence of a partial pneumothorax, tug upon lung tissue over a bleeding vessel and prevent its closing. Sauerbruch rarely operates for a first severe hemorrhage. Pribram advises trying the minor phrenicotomy before using more severe measures. Stöcklin advises pneumolysis with paraffin "fill," in preference to a thoracoplasty, as: (1) it is a less severe operation; (2) there is less chance of suffocation if another large hemorrhage occurs and the mechanical conditions for expectoration are better; (3) greater pressure can be exerted upon the bleeding vessel, if the mediastinum is well fixed. Sauerbruch does his typical paravertebral thoracoplasty if the hemorrhages have been small and the patient is in good condition, but if not, he resects portions of only ribs I, II and III paravertebrally, then strips the pleura from the ribs and packs with a gauze tampon. Forty-two of Stöcklin's 100 thoracoplasties had had hemoptysis prior to operation, but he never saw it recur during operation, although 4 patients bled from upper lobe cavities several days after first stage operation, when the lower ribs were resected, developed aspiration pneumonia in the better lung and 2 of them died.

The So-called "Good" or Better Lung. Inability to foretell accurately whether or not the disease that exists in the so-called "good lung" will progress after operation is the chief hindrance to an accurate selection of cases for operation. Among the 824 patients of my collected series who were judiciously selected for operation and managed in accordance with the best known methods, only 143 (17 per cent) died after the first postoperative month, whereas 55 (27.5 per cent) of the 200 patients, who were not so carefully selected and managed, died after the first postoperative month. Bull calls the "good" lung "the sword of Damocles." Brauer finds that from 10 to 15 per cent of those who have been operated upon show progression of the lesions in the better lung, usually to death. This progression may be accounted for by; (1) the increased work the better lung is called upon to do after the other lung is shut out from function; (2) the normal tendency of much tuberculous disease toward progression; (3) activation by massive "auto-tuberculinization," the result of sudden squeezing out of toxins from the worse lung at operation. Pathologically it is a great rarity to find any considerable disease in one lung and literally none in the other, although strictly unilateral disease may be not infrequent clinically. In general, most clinicians of experience are agreed that if tuberculosis is demonstrable by roentgen-ray or physical examination in the better lung, it must be only of small extent and limited to the

apex, and non-progressive during an observation period of several months. Sauerbruch, Brauer, Bull and Stöcklin, Bérard and Dumarest, men of the widest experience, say that any lesions in the better lung must be absolutely inactive, that is, quiescent or arrested. Jacobaeus and Key state that the size of the lesions is of less importance than the degree of their activity, and that old shrunken lesions offer the best prognosis. Lorey says that the better lung must be "practically sound." Sauerbruch believes that the clinical signs are of greater importance than the roentgen-ray in judging clinical activity in the better lung, and, of course, urges a careful combination of the two methods; if in doubt he advises prolonged observation in a sanitorium; Jacobaeus and Key say for six months; Archibald advises six to twelve months sanitorium observation of the better lung before performing the second stage, if it has shown suspicious signs after the first stage. Sauerbruch has proposed a preliminary phrenicotomy on the worse side in cases of doubt as to tuberculous activity of the better. This throws a small amount of extra work upon the better lung, and lesions with tendency toward activity are very apt to light up temporarily and thus warn against performance of the major operation. If they remained unchanged for two to three weeks thoracoplasty may be undertaken (Fischer). Sauerbruch and others have found this functional test of great value, and it has the further advantage of causing some improvement and rest of the worse side, thereby putting the patient in better condition for a thoracoplasty, if found indicated.

If apprehension is felt about permanently throwing upon the better lung even the slightly increased work that contralateral phrenicotomy does, use may be made of a procedure that Fischer practises as a test of the better lung before performing definitive phrenicotomy. The accessory phrenic nerve is partially resected and a 1 mm. wide tube of ice (Perthes) held against a 2 to 3 mm. length of the main phrenic stem for fifteen seconds. This produces only temporary diaphragmatic paralysis, and if the lesions in the better lung do not become activated within the next three weeks permanent phrenicotomy and thoracoplasty, or thoracoplasty alone may be done. From experiments upon rabbits Balderry found that if the phrenic stem is sprayed with ethyl chloride for ninety seconds (which frosts the nerve for forty-five seconds) there follows an immediate diminution in diaphragmatic motion, which becomes more marked at ten hours; electric stimulation of the nerve ten to fourteen days after the freezing causes no diaphragmatic contraction, but within five to seven weeks motion returns.

As the validity of the better lung is of great importance to the economy after the other lung has been permanently prevented from functioning, it must be sound in all respects—without bronchitis, bronchiectasis, asthma, pleural pain or extensive adhesions that might restrict respiration.

There is a rapidly increasing tendency to use pneumothorax upon patients whose better lung shows definite tuberculous activity of the upper lobe, upon the theory that by eliminating the grossly diseased, worse lung as the main source of toxin formation, the lesser lesions are enabled to use the whole of the body's resistance for recovery. This action is comparable to the improvement of pulmonary lesions after the resection of a tuberculous joint, and of the better of two kidneys after the removal of the worse. Of Matson's 480 artificial pneumothoraces 282 had demonstrable disease on the better side, and yet, during treatment, progression occurred in only 35 of them (12.4 per cent). As the principle is the same for surgical as for gas compression, except that the physiological changes are produced more abruptly, there is a definite tendency among many surgeons to be more lenient as to demanding absolute inactivity in the better lung as a prerequisite for operation. Eloesser says that the better lung need not be absolutely sound—"no large cavity or evident active area" that would be apt to light up. Davies and Jessen say that the lesions must not be extensive or acutely active. Saugmann operated in the presence of some "badness," and in all of his 40 cases there was some, as in all of Archibald's first 15. If there is more than a little active disease on the good side, and if thoracoplasty is the only hope, Brauer and Gravensen would operate if there were no other definite contraindication; some improvement may be expected. Both Saugmann and Sauerbruch have obtained improvement when the better side was considerably involved at the time of operation, but warn that pleasant surprises are far less frequent than unpleasant ones. Sauerbruch pleads against the operation *ut aliquid fiat;* in the final stages of consumption patients and their families are inclined to beg for any last chance, but operation in the presence of definite contraindications only makes death worse because of suffocation from insufficient lung ventilation, and pain. As a rule Sauerbruch will operate in the presence of activity in the better lung only when the worse lung has been almost entirely destroyed, and where the respiration in the better lung has compensated.

The smallest active lesion in either the hilus or lower lobe of the better lung absolutely contraindicates operation for Sauerbruch and Stöcklin. Brauer will not operate if there is "a small lesion at the base or a larger one at the hilus," nor will Bull if there is any lesion at all, old or recent, at the base. On the other hand, Jacobaeus and Key do not hesitate to operate if small lesions at the "good" hilus or base are relatively inactive; they have operated upon 9 patients with roentgen-ray or auscultatory evidence of tuberculosis in the lower half of the "good" lung, and 7 of them were improved.

Next in importance in deciding for or against operation is the condition of the cariovascular system. One-half of Stöcklin's

operative deaths occurred from heart failure, and now he refuses to operate if he is in doubt as to the soundness of the heart. Even compensated valvular lesions are contraindications for Madinier. The lung fibrosis in tuberculosis does tax the right heart to some extent, and the operative compression of the lung makes further demands upon it. Careful functional tests of the cardiovascular system are essential for sound judgment of a patient's suitability for operation.

Sauerbruch, Brauer and Bull have called attention to those cases of cardiac distress and dyspnea due to extreme displacement of the heart and trachea toward the side of an adherent, shrunken lung, and to the great relief afforded by an ordinary thoracoplasty, which acts in the manner of a cardiolysis. When its effect is insufficient Sauerbruch performs a classical cardiolysis, removing the periosteum with the ribs.

Bones and Joints. Bull considers thoracoplasty contraindicated in the presence of any bone or joint tuberculosis; von Muralt in the presence of Pott's disease. Stöcklin says that a single bone lesion should not contraindicate.

Insanity. Sauerbruch warns against psychotic tendencies, as they might develop postoperatively and cause the patient to tear open his wound, to insist on exercising, or to refuse to expectorate. However, curable psychoses do not necessarily contraindicate operation.

Pregnancy. Artificial pneumothorax has been initiated during pregnancy, with satisfactory results. If adhesions should prevent the use of pneumothorax, a therapeutic abortion should take precedence over thoracoplasty.

Larynx. There is general agreement that mild and midsevere laryngeal tuberculosis almost always improves after thoracoplasty. Brauer says that deep disease is a contraindication, but Saugmann said that acute progressive disease is not a definite contraindication, as without operation such patients are certain to die.

Kidney. Any organic nephritis, including amyloid degeneration, contraindicates thoracoplasty (Brauer; Stöcklin); von Muralt said that mild amyloid is favorably influenced. Any renal tuberculosis contraindicates, according to Brauer and Bull, although Stöcklin states that unilateral renal tuberculosis does not contraindicate, and Jessen says that it merely decreases the chances of clinical success. The milder grades of diabetes do not contraindicate, but the severer ones absolutely do.

Intestines. Every continental author absolutely condemns operation when there is the least tuberculous involvement of the intestines, with the possible exception of ischiorectal disease. Matson *et al.* say it does not contraindicate pneumothorax therapy if it is not so severe as to interfere with proper nutrition. As a

result of the rapid strides being made in the treatment of intestinal tuberculosis with heliotherapy, it may be that minimal intestinal involvement will soon be considered not to be a definite contra-indication.

VI. Choice of Operation. Many variables as to type and location of lesions and as to the general clinical condition of the patient, combine to make it obviously impossible to present any hard-and-fast rules as to choice of operative technic.

It may be said that, in general, most cases for whom operation is indicated will do best after a two-stage "Sauerbruch," or a two-stage "Brauer." As the compression from the latter is the greater of the two, it is indicated for those whose lesions are extensive, and whose general condition is sufficiently good to withstand the somewhat more severe operation. It will be found in a certain minority of cases operated upon by either technic, that the compression has not been sufficient to control the disease; this is especially true of thick-walled cavities and infiltrative lesions that are unusually stiff. It then becomes necessary to supplement the original operation by further removal of ribs posteriorly, or parasternally, or by pneumolysis. The most commonly used supplementary procedure is pneumolysis, which is an extrapleural separation of the lung and both of its pleuræ from the ribs, and a filling of the space created with a gauze tampon, or a fat graft, a paraffine "fill," or a pedicled muscle graft. When even these measures fail to collapse certain cavities, cavity drainage is indicated. Favorable mention has already been made of the use of phrenicotomy as a preliminary to any type of operation.

Partial Procedures. Resection of parts of ribs I to XI is known as the complete operation, in that it compresses an entire hemithorax and puts it at rest. Primary operations that compress only a part of a hemithorax (over the principal lesions) are termed partial procedures. They include resection of only the upper or lower five or seven ribs; pneumolysis; phrenicotomy.

Where the tuberculous lesions are apparently chiefly confined to the upper lobe, the temptation is great to limit the compression to that region and thus to save the lower lobe for function and so to spare the better lung any increased work that might activate a quiescent disease process there. Until very recent years this practice has been relatively common, but increasingly frequent reports of its unfavorable late results, and Sauerbruch's impassioned pleas against it, have combined to put it in disrepute, except for very particularly indicated cases. Sauerbruch, Brauer, L. Spengler and Saugmann, Jessen, Hauke and Goetze warn against it on the basis of their unfavorable results. Eloesser puts it neatly by saying that the complete operation should always be done primarily, for to trust to half-measures is often to lose the opportunity to control

the lesions during a favorable stage. Bull advises complete operation even if the disease seems to be limited entirely to the lower lobe; in such a case the *first* stage of the operation would be the resection of the *upper* ribs in order to prevent aspiration above. Gravensen, on the other hand, favors limiting the resections to the lower ribs if only the lower lung is diseased.

The principal objections to partial operations are: (1) abrupt compression of the most diseased portion of a lung squeezes out infective material, which is liable to be aspirated into that part of the same lung which is not compressed and is actively breathing, and disease spread. Sauerbruch has seen this occur not infrequently after partial procedures, and is now uncompromisingly opposed to them. Stöcklin says it occurs once in 100 cases. L. Spengler believes that not many of these cases of aspiration pneumonia have as yet been reported by publication. Baer personally has never seen a case of aspiration. While complete operation does not absolutely assure against aspiration, it very greatly reduces its incidence. Davies advises phrenicotomy preliminary to pneumolysis. (2) Brauer says that the lower lobe of a lung, in which surgical compression is indicated for upper lobe disease, almost always contains a few active tubercles, although they may not be demonstrable clinically; and that the extra work imposed upon such a lobe may determine a rapid advance of the disease there, so that a difficult and dangerous secondary operation, involving removal of regenerated bone in the field of the first operation, would then become necessary. Wilms and Sauerbruch would always compress the lower lobe, even if not apparently diseased. (3) Compression of only a part of one lung allows that part to "slip" to the unnarrowed space of the chest cavity, and the final effect is that the whole lung is relaxed, rather than the most diseased parts being actually compressed, and this is not so favorable for healing. This does not occur to such a degree if there are strong pleural adhesions, and if the mediastinum is well fixed for counterpressure. (4) If the continuity of any one or more ribs (ribs XI and XII excepted) remains uninterrupted, this rib, or ribs, acts as a support for the whole hemithorax and prevents its "settling" and compressing the lung as well as it does after a complete thoracoplasty. (5) As thoracic movement on the diseased side is only partially restricted, the flow of lymph into the general circulation is only partially checked (Jessen). (6) A ridge, which is the uppermost of the remaining ribs and marks the lower limit of an upper partial thoracoplasty, may become so painful as to require its removal, or the removal of all the remaining ribs.

Partial procedures, however, have certain advantages and rare indications. They are: (1) For patients whose lesions are limited to a small area, are non-progressive in character and have shrunken

to such a degree as to demand release of tension by resection of the resisting overlying bony cage; such patients, however, should not be producing more than 20 to 30 cc of sputum a day, else the danger of aspiration to the uncompressed part of the lung is considerable. For such cases Sauerbruch would be willing to resect only the upper ribs, although he would be strongly tempted to play safe and first section the lower ribs in order to check their movements, or he might first do a phrenicotomy. (2) Patients who are too sick to withstand the operative shock of the complete operation may bear a partial operation very well, and its favorable influence may justify the risks of the partial procedure. Its advantages in such cases are the less operative shock, less mediastinal displacement, less interference with circulation and respiration; postoperative cough and expectoration are easier. This last named advantage especially indicates partial operation for severe hemoptyses where the danger of spread of infection by aspiration is always great; for these cases Sauerbruch resects ribs I, II and III parasternally, performs a pneumolysis and places a snug gauze tampon. A phrenicotomy alone may check hemoptysis. (3) Certain patients may have so much active disease on the better side that the extra work that would be imposed upon it by a complete operation on the worse side would probably cause its rapid spread; in them partial compression on the worse side may bring about so much improvement of general resistance as to enable the better lung to heal itself, and then if the worse lung is still active, the operation may be safely completed. (4) Wilms would resect the three upper ribs on each side for strictly circumscribed, relatively inactive, bilateral apical disease, if it had marked fibrotic tendencies and if there were very little sputum.

Further description of pneumolysis and of phrenicotomy will be found below, where they are discussed as operations supplementary to thoracoplasty.

VII. Preoperative Management. Saugmann and Madinier strongly advise that all operations for pulmonary tuberculosis be performed at suitably equipped sanitoria and not at general hospitals, which are usually in the city, and to which patients with little reserve strength must be transported, and where the conditions are rarely favorable for suitable tuberculosis régime.

If operation has been decided upon and there is some question as to the functional validity of the heart, a preoperative course of digitalis is to be highly recommended.

Bed rest for at least two weeks is advisable for patients who present themselves for operation with a simple chronic bronchitis; inhalants and expectorants may prove of use.

A very important prophylactic measure against aspiration of infected secretions, especially from cavities, during operation is to insist that the patient "empty his lung" two hours, and again one

hour before operation; this he does by assuming the position, best known to himself, that enables him to cough up all loose sputum in a few minutes. Sometimes the best position is leaning over the side of the bed, to drain the sputum by gravity; sometimes lying on the better side and sometimes on the worse.

Broad experience has taught both Sauerbruch and Jessen to fear greater preoperative doses of morphin than $\frac{1}{6}$ gr. (0.0108 gm.) when a local anesthetic is to be used in addition; they fear synergistic action.

Other preoperative preparation does not differ from that used for general major surgery.

VIII. Anesthesia. Choice of anesthetic is somewhat influenced by national custom. For general narcosis ether, or ether-chloroform mixture is commonly used on the continent; nitrous-oxide-oxygen in America. In all countries, however, regional and local anesthesia is used most, or in connection with general narcosis. Sauerbruch and Bérard would refuse to operate at all if a patient were found to be hypersusceptible to a combination of morphin and novocain, and whose heart or great amount of sputum contraindicated general narcosis.

Sauerbruch's preference is for straight ether whenever there are less than 30 cc of sputum a day (or a little more than this if it can be well evacuated just before operation); its use upon many hundreds of patients with active pulmonary tuberculosis has convinced him that it has no unfavorable action on the lungs, unless by abolishing the cough reflex it allows aspiration of secretions. This, of course, would hold for a like degree of narcosis with any other general anesthetic, and sudden groaning or crying under an imperfect local anesthesia may also be responsible for aspiration. As a great majority of cases for thoracoplasty have more than 30 cc of sputum per day, Sauerbruch is obliged to use regional and local anesthesia far more often than general, and to his regret as he has learned to fear the toxic action of the amounts of novocain required for these operations. He has seen a fatal case of poisoning from novocain, and 2 cases of dangerous collapse from which there was recovery within twenty-four to forty-eight hours, and a number of cases of mild poisoning. At first he attributed the symptoms of this collapse—pallor, light cyanosis, sweating, slow then fast pulse, cold nose, hiccough, vomiting—to operative shock, but experience has showed him that there is a difference, and that when the indications for operation are properly placed there is almost no true operative shock.

Sauerbruch limits himself to 0.9 gm. of novocain, and to this amount he adds 0.001 cc of adrenalin chloride; he makes the solutions isotonic with the blood, as anesthesia then lasts longer. He infiltrates the line of incision with 50 cc of 0.5 per cent solution,

using a 12 cm. long needle; then by the Schumaker technic he injects 5 to 6 cc of a 1 per cent solution around each of the intercostal nerves at the rib angles. Except in rare cases he is able to obtain practically complete anesthesia. Archibald recommends injecting each intercostal nerve, after the ribs have been exposed, at two or three points near the rib angle in order to increase the chances of obtaining complete anesthesia. Saugmann found it more accurate to inject the anesthetic around the intercostal nerves after the skin-muscle incision had been made. Baer does this for the upper nerves, as he fears he might wound the pleura or lung and thereby spread infection, if he attempted to reach them all the way from the skin; Guilliminet recommends diffusing the anesthetic solution by gently stroking the tissues over the place of injection. Davies has suggested the use of anoci-association. Shumacker was able to produce perfect regional anesthesia in only 14 of 35 cases. In addition to his cases of poisoning Sauerbruch has reported 2 fatal accidents; one was a suppurative mediastinitis consequent upon carrying infection on the needle from latent infection in the pleura; the other was a ruptured aneurysm which was started by a wound from the anesthetizing needle.

Saugmann always tested the patient's susceptibility to novocain a few days before operation. He reported a death following the use of 190 cc of a 0.5 per cent novocain, plus 0.015 gm. morphin one-half hour before operation. He always tried to limit himself to 150 cc of 0.5 per cent solution, and set 200 cc as the absolute limit. Where there is only a small amount of sputum he would not hesitate to use a little ether. Eloesser and Bull also warn against hypersusceptibility to novocain.

Stöcklin reports a death from the use of 1.2 gm. novocain, and now uses morphin and scopolamin and from 0.5 to 0.7 gm. novocain. Lorey uses as much as 150 to 200 cc 1 per cent solution, and Bull up to 300 cc 0.5 per cent plus 50 to 75 cc 1 per cent. Willy Meyer reports a death in forty-eight hours, probably from novocain poisoning; he now fears the Kappis method of injecting the anesthetic in the region of the intervertebral foramina, and will use only the Shumacker technic of injecting near the rib angles. Meeker and Frazer conclude from a study of regional-local anesthesia in 4000 general surgical cases that 1.5 to 2 gm. 0.5 per cent novocain-adrenalin solution are safe for local infiltration, or 1 gm. of 1 per cent novocain-adrenalin is safe for nerve block. Bérard is pleased with the use of anacain, which is used with adrenalin in the same strengths as novocain; as much as 1.2 gm. may be employed. Its great advantage is that it maintains anesthesia for thirty-six to forty-eight hours; this covers the most painful postoperative period, and further, permits the injection of the anesthetic to be made an hour or so before the operation.

(To be continued)

REVIEWS.

A Diabetic Manual for the Mutual Use of Doctor and Patient. By Elliott P. Joslin, M.D., Clinical Professor of Medicine, Harvard Medical School, Consulting Physician, Boston City Hospital. Third edition. Pp. 211; 17 illustrations. Philadelphia: Lea & Febiger, 1924.

The close coöperation that the physician who is treating diabetes has with his patient is seen in almost no other disease, and probably in no other disease does the physician go to the same extent to teach the individual about the disease, as in diabetes. For this reason any book which explains in simplified language just what the diabetic is to do is of great service in aiding patient and physician in understanding and in following out the course of the disease. For this reason several books of this type now on the market are extremely popular, but the one in question has always been among the most popular, probably because of the fame of the author as a diabetic specialist as well as the deep scientific knowledge that he possesses and which he is able to present to the public in a way which appeals most thoroughly. This little book of Joslin's is excellent in every way. It needs no introduction to the medical profession, and the profession can always feel that it is the most satisfactory book of this type on the market. M.

Medical and Sanitary Inspection of Schools for the Health Officer, the Physician, the Nurse and the Teacher. By S. W. Newmayer, A.B., M.D., Supervisor of School Medical Inspection, Philadelphia. Second edition. Pp. 462; 79 illustrations and 6 plates. Philadelphia and New York: Lea & Febiger, 1924.

A number of modifications have been made in the original text, to keep abreast of recent developments in the various fields of school inspection. The book as it stands is a practical and comprehensive handbook which will highly commend itself to officials whose care is the health of school children. A.

TUBERCULOSIS OF THE LARYNX. By SIR ST. CLAIR THOMSON, M.D., F.C.R.P., F.R.C.S. Pp. 91; 7 illustrations. London: Medical Research Council, 1924.

THIS is a very complete exposition of the subject. It goes into detail concerning various phases of laryngeal tuberculosis and is compiled with the usual thoroughness of the work put out by the Medical Research Council. It is a most complete exposition by one who has seen and observed with a critical mind many cases of tuberculosis of the larynx.

M.

DIFFERENTIAL DIAGNOSIS. Vol. II. By RICHARD C. CABOT, M.D., Professor of Medicine and Professor of Social Ethics at Harvard University; formerly Chief of West Medical Service at the Massachusetts General Hospital. Third edition. Pp. 709; 254 illustrations. Philadelphia: W. B. Saunders Company, 1924.

THE third edition of this well-known, unusual presentation of differential diagnosis remains essentially unchanged from that of the previous editions in form, in material presented and in the case histories. The introductory discussion, however, has been changed somewhat and, to use the hackneyed expression, the book has been brought up to date. To those of the medical profession not familiar with this particular book by the author it may be said that it is an extremely interesting presentation of the subject of differential diagnosis. It makes extremely smooth and easy reading, as would be expected from one who has the gift of writing as has the author; and because of this ease of expression the reader unconsciously learns a great deal while perusing the book which he would otherwise miss in a presentation less clear and less succinct.

M.

DIPHTHERIA. ITS BACTERIOLOGY, PATHOLOGY AND IMMUNOLOGY. By FREDERICK W. ANDREWES, WILLIAM BULLOCH, S. R. DOUGLAS, GEORGES DREYER, A. D. GARDNER, PAUL FILDES, J. C. G. LEDINGHAM and C. G. L. WOLF. Pp. 544; 6 illustrations. London: Medical Research Council, 1923.

THE present monograph published by the Medical Research Council is a decided departure from the usual presentation of a scientific subject. It is the work of seven men, each one of whom, although contributing only special chapters, has gone over in detail the other chapters, so that they have become collectively

responsible for each chapter. The literature of diphtheria has been gone over most thoroughly. Every reference available on the scientific side of the disease has been utilized and each article has been critically read. Those that were of no value were discarded, whereas the valuable ones were incorporated in the work. The number of articles that were utilized may be appreciated by the fact that there are over a hundred pages of references in the bibliography. In addition to this very complete critical review of the literature of diphtheria, the authors have been enabled by the British Medical Research Council to take up research problems in order to elucidate, if possible, work which was incomplete or fill in the gaps in our knowledge. In this way the Committee on Publication has brought together a monograph which seems to be the ultimate in completeness. That it will be of great value to the research worker and the scientist as well as the medical profession in general goes without saying. The reviewer is most enthusiastic about the work, and trusts that the Medical Research Council will in the future take up in the same way other of the acute infectious diseases. M.

DICTIONARY OF BOTANICAL EQUIVALENTS. By ERNST ARTSCHWAGER, PH.D., Instructor in Plant Physiology, Cornell University; and EDWINA M. SMILEY, M.A., Instructor in Plant Pathology, Cornell University. Pp. 137. Baltimore: Williams & Wilkins Co., 1924.

THIS small dictionary is especially for the use of the botanist and the pharmacologist. It contains the German and French terms with their English translation. A needed dictionary is now added to the list of standard dictionaries. M.

THE ENDOCRINE ORGANS. Part I. By E. SHARPEY-SCHAFER, LL.D., D.Sc., M.D., F.R.S., Professor of Physiology, Edinburgh University. Second edition. Pp. 175; 86 illustrations. New York: Longmans, Greene & Co., 1924.

THE first portion of this work which is now making its appearance discusses diseases of the thyroid, parathyroid and suprarenal. This second edition, appearing nine years after the first edition, is very thoroughly revised, so fully, indeed, that it might almost be considered a new treatise on the subject of endocrinology. The book is a physiological rather than a clinical study, and deals with physiological experiments rather than hypothetical results in the

treatment of presumed endocrine disorder. Definite proof is brought for every statement that the author makes, and hence the work is authoritative to the fullest extent. M.

PATHOLOGISCH-PHYSIOLOGISCHE PROPÄDEUTIK. By MAX BURGER, a.o. Professor der inneren Medizin und Oberarzt an der med. Universitäts Klinik Kiel; with a foreword by A. SCHITTENHELM, Direktor der Klinik. Pp. 342; 27 illustrations. Berlin: Julius Springer, 1924.

RECOGNIZING Krehl's celebrated book on pathological physiology as unique of its kind, the author of this new book aims for a new goal, namely, to offer to students and young doctors an introduction into pathological physiology which will clarify the difficult problems of the clinic and its borderline. In the present instance, however, this is largely a distinction rather than a difference, as much the same topics are taken up in much the same way as in Krehl's book. To be sure, a few more subjects are considered (functional disturbances of endocrines, liver, spleen, skin and organs of locomotion), but to offset this the others are treated less thoroughly, in poorer sequence and not so well. In the section on diabetes the only mention of insulin is a reference to MacLeod's paper on the fish source of insulin, which is cited from a 1923 German referate; in the section on the hypophysis no mention is made of the recent work on the relation of the hypothalamic region to hypophyseal symptoms and in fact only one reference is less than ten years old; in the section on the spleen the references are without exception to German authors and make many assertions which are incorrect or, at best, quite undecided. We agree with the introducer that Krehl's book remains in its former position.

K.

APPLIED PATHOLOGY IN DISEASES OF THE NOSE, THROAT AND EAR. By JOSEPH C. BECK, M.D., F.A.C.S., Associate Professor of Laryngology, Rhinology and Otology, University of Illinois, College of Medicine. First edition. Pp. 280; 268 illustrations. St. Louis: C. V. Mosby Company, 1923.

To the average medical reader the term "applied pathology" is not a very definite concept and the book under review will not contribute toward its clarification. The author's method has been to consider in twelve chapters one hundred and twenty acute and chronic diseases of the nose, throat and ear, in sections varying

from a paragraph to several pages in length. Usually the only subheading is "Treatment," but in a few "Gross Pathology" (which not infrequently wanders into symptoms and so forth), and even "Histopathology" and "Application" are segregated. Except for this and a rather liberal use of photomicrographs, the book would be more accurately described as an incomplete text-book on the subject. The complaint of incompleteness is met in the foreword by the author's expressed "desire to limit this work almost exclusively to my personal experience." K.

LOUIS PASTEUR. By S. J. HOLMES, PH.D., Professor of Zoölogy, University of California. Pp. 246; 14 illustrations. New York: Harcourt, Brace & Co., 1924.

THIS small biography of Pasteur, as the author remarks in his preface, is in no way an attempt to offer anything new to what has already been written, but it does present in a simple informat ve and pleasing manner the important milestones in the life of this great man. It may be read with enjoyment by any individual who has the slightest knowledge of any type of science, or by one who is interested in science. M.

OUTLINES OF MEDICAL HYDROLOGY. By R. FORTESCUE FOX, M.D. Pp. 136; 10 illustrations. London: J. and A. Churchill, 1924.

HYDROLOGY is a branch of therapeutics which is very extensively neglected in this country. It might be well for practitioners to look over the series of lectures by the author, delivered at the University of London, which describes in detail the various types of baths and their indications. The book is well written and conservative, and the author does not claim success in every type of disease or disorder, as do so many of the men who ride therapeutic hobbies. M.

MANAGEMENT OF DIABETES. By GEORGE A. HARROP, JR., Associate in Medicine, College of Physicians and Surgeons, Columbia University and Assistant Visiting Physician, Presbyterian Hospital, New York. Pp. 176. New York: Paul B. Hoeber, Inc., 1924.

HARROP has summarized the clinical instruction and laboratory instruction that has been given at the Presbyterian Hospital in

New York to physicians unacquainted with the use of insulin. He has put this information in a more complete form than any of the small books on diabetes with which we are acquainted, and he has given extremely wise advice to the physicians. Included in the book are almost fifty pages of diabetic recipes, as well as a rather unusual summary of food values of the standard foods. The tyro in the handling of diabetes can well profit by a close study of this most agreeable presentation of the subject.

M.

HEMORRHOIDS, THEIR ETIOLOGY, PROPHYLAXIS AND TREATMENT BY MEANS OF INJECTIONS. By ARTHUR S. MORLEY, F.R.C.S. (ENG.), late Temporary Assistant Surgeon to St. Mark's Hospital for Cancer, Fistula and Other Diseases of the Rectum. Pp. 114. London: Henry Frowde, Hodder & Stoughton, 1924.

THIS book is devoted to the thesis that the best treatment for uncomplicated internal hemorrhoids is by the injection method. Its contents, therefore, are rather controversial than judicial. He apparently has no extended experience with operation to parallel his large series of injections and in handling the statistics from St. Mark's Hospital in London; as to the mortality and morbidity of operation, he fails to point out that many of these cases were severe and of a type unsuited for injection. The book really serves to reiterate what was already known, that under proper precautions simple internal hemorrhoids can be successfully treated in many cases by injection.

P.

THE CIRCULATORY DISTURBANCES OF THE EXTREMITIES, INCLUDING GANGRENE, VASOMOTOR AND TROPHIC DISORDERS. By LEO BUERGER, M.A., M.D. Pp. 628; 192 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

IN recent years considerable new material upon the circulation of the extremities has made its appearance. Direct microscopic examination of the capillaries has been found to be a useful and simple procedure; studies upon the anatomy and physiology of these vessels have been published by Krogh and others, and the role of the sympathetic and autonomic nervous systems in circulatory disturbances has been extensively studied. These and other studies have resulted in a renewal of interest in Raynaud's disease, Buerger's disease, erythromelalgia and other circulatory diseases of the extremities. The author has gathered from widely divergent sources the best available data upon these subjects, and assembled them into

a book which in addition to being readable, is a veritable storehouse of information. This book constitutes a distinctly valuable contribution by one whose authority in this field will hardly be questioned. A.

AIDS TO MEDICAL DIAGNOSIS. By ARTHUR WHITING, M.D., Senior Physician to the Prince of Wales' General Hospital, Tottenham, London, and late Physician to the Mount Vernon Hospital for Consumption and Diseases of the Chest. Pp. 177; 16 illustrations. Third edition. New York: William Wood & Co., 1924.

THIS little book is replete with practical points in the diagnosis of the usual conditions which a medical student meets in the wards and dispensaries. The author makes no attempt to discuss systematically the various diagnoses, but does give the more asserting features in the several diseases. M.

DIABETES. By PHILIP HOROWITZ, M.D. Second edition. Pp. 219; 34 illustrations. New York: Paul B. Hoeber, Inc., 1924.

THE reviewer has employed the small book of the author's for several years, and has found the previous edition extremely valuable not only for his own use, but also in letting diabetic patients with sufficiently educated minds read it over to their own great advantage. The new edition, of course, contains the more important additions brought about by the introduction of insulin in the therapy of diabetes. M.

BULLETIN NO. X OF THE INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUM. Pp. 165; 39 illustrations. New York: P. B. Hoeber, 1924.

THE bulletin of this Society, which is also a journal of technical methods, is under the editorial management of Dr. Maude Abbott and Major Coupal. It contains not only general and special articles on gross and histological morbid anatomy, but also an experience department, valuable sections on museum, bacteriological, microscopic and photographic technic, amplified by abstracts of the current literature on these topics. The list of members shows its truly international character, and it is hoped that the European sections will soon become as active as their American and Canadian confrères. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Rectal Digitalis Therapy.—LEVY (*Arch. Int. Med.*, 1924, **33**, 742) reports a series of 19 patients with auricular fibrillation and 1 patient with ectopic auricular tachycardia, to whom an aqueous solution of purified extract of digitalis leaves was given by rectum in doses ranging from 8 to 20 cc. Unmistakable initial effects on the heart-rate was noticed in an average time of two hours and thirty-five minutes. The average time of maximum effect was reached in nine hours and thirty minutes. The initial effect was seen on an average in two hours and a half. The author reports that in every case a desirable therapeutic effect was obtained. In some of the patients results were dramatically rapid. While the author says that this type of therapy is intended to supplement, not supplant, the oral method of administration, and is useful in cases with nausea and vomiting, he intends to convey the meaning that the nausea and vomiting must be due to some cause other than the result of the digitalis therapy, for it is well known that the effect of digitalis is central and not peripheral and digitalis nausea may occur after the administration of digitalis by any method. After a surgical operation in a patient who has need of digitalis the rectal administration of the drug is most satisfactory.

A Study of Mixed Leukemia, with the Report of a Case.—The occurrence of mixed leukemia is extremely rare, so rare indeed that some hematologists doubt if there is such an entity. LOGEFEIL (*Arch. Int. Med.*, 1924, **33**, 659) has what he believes to be another one of the rare cases which have been rarely described. He appreciates the fact that some hematologists question the possibility of there being a true

mixed leukemia, and he discusses this fully in his case report, in which the blood smears as well as the histological study of the tissues showed activity of both myeloid and lymphoid systems. While hematologists quite generally do recognize the possibility of such occurrence, nevertheless it must be borne in mind in such a case as the author's, occurring as it did in a small child, that a marked lymphoid reaction is very frequent in children and that this reaction may be sufficiently severe as to lead one to the opinion that leukemia is present.

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l. **Hitherto Undescribed Form of Valvular and Mural Endocarditis.** —LIBMAN, whose work on endocarditis needs no introduction to the medical profession, and SACKS (*Arch. Int. Med.*, 1924, **33**, 701), in a long and complete paper, discuss fully a new type of endocarditis. The importance of their contribution make it necessary to include a summary of their results: "We have had the opportunity of studying the clinical and pathological findings in 4 cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. In morphology and localization the endocardial lesions differed from those observed in subacute bacterial, rheumatic and other types of endocarditis. All four valves were involved, and there was a tendency for the inflammatory process to attack the mural endocardium. A uniform finding in our cases was the extension of the endocarditic process from the ventricular aspect of the posterior cusp of the mitral valve along the adjacent mural endocardium of the posterior wall of the ventricle. Isolated areas of mural endocarditis were found in the right auricle and both ventricles. The vegetations were free of demonstrable bacteria, and presented a histological structure which differed in many respects from that of the lesions in other types of endocarditis. The heart muscle showed neither Aschoff bodies nor Bracht-Waechter lesions, and the kidneys showed no embolic glomerular lesions. The disease, in the form in which it attacked young people who had previously had no organic symptoms, ran a subacute course with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiæ, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. One of the patients is said to have had tender erythematous nodules, which were apparently identical with the Osler nodes, previously observed only in subacute bacterial endocarditis. For reasons stated above the acute pericarditis, white-centered petechiæ and negative blood cultures together appears to have diagnostic value, especially in differentiating these cases from rheumatic and subacute bacterial endocarditis. In certain cases the chief diagnostic problem appears to be the detection of endocarditis, for the manifestations of the latter may be masked by other symptoms. In such cases the presence of an eruption on the face resembling acute lupus erythematosus disseminatus or peculiar erythematous and purpuric rashes else-

where should lead to a search for the other manifestations of the atypical form of endocarditis. Attention was directed to the similarity of certain of the symptoms to those observed in the erythema group of Osler and to the existence of a possible relationship between certain instances of the latter and the atypical form of endocarditis. The frequency of the disease and the ultimate outcome of non-fatal cases is a matter of conjecture. Future studies must determine whether this form of endocarditis is a potential cause of chronic valvular disease. The etiology is as yet unknown, and it is suggested that in future studies the special methods adopted for a cultivation of filtrable viruses and spirochetes be employed among others in the search for the exciting agent."

A Study of the Mechanism of Absorption of Substances from the Nasopharynx.—BLUMGART (*Arch. Int. Med.*, 1924, **33**, 415), using the method by which Meed demonstrated the passage of the cerebrospinal fluid into the lymphatics of the brain has been able to show a rapid absorption of crystalloid, colloid, and certain forms of particulate matter through the olfactory epithelium. The route of passage of the absorbed substances be found to be only along the olfactory nerve cells into the region of the lymphatics. These experimental findings accord well with those on the mode of infection in meningitis and poliomyelitis. It is suggested that such ready absorption along the olfactory cells is a physiological adaptation to bring to these cells the substances of the air which we are to perceive through our sense of smell.

Studies on the Respiratory Mechanism in Lobar Pneumonia: A Study of Lung Volume in Relation to the Clinical Course of the Disease.—BINGER and BRAU (*Jour. Exper. Med.*, 1924, **39**, 677) studied the functional residual air in a series of normal patients and in 10 patients with lobar pneumonia at different stages of the disease. Their purpose in mind was to obtain data concerning the relationship in pneumonia between the extent and progress of pulmonary involvement, the occurrence of dyspnea and cyanosis and the changes in lung volume. A constant relationship was found to exist between the persistence and disappearance of symptoms (fever, accelerated heart-rate, rapid and shallow breathing, cyanosis) and fluctuations in the functional residual air. The residual air was found to be decreased whenever the above symptoms persisted, while it rose toward normal as they disappeared. This rise was usually to be noticed soon after the crisis. The reduction in residual lung volume was also found to parallel the alterations in physical signs and radiographical shadows. As these pathological signs cleared up the residual lung volume returned toward normal. From the time of onset of the disease eleven to twelve days were required, on the average, for the functional residual air to become constant in the cases which recovered.

SURGERY

UNDER THE CHARGE OF

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Results of Treatment following Compound Fractures Occurring in Civil Life.—Cook (*Jour. Bone and Joint Surg.*, 1924, **6**, 93) says that death occurred in 3 cases by the method of aseptic occlusion; 2 of septicemia and 1 of a gas bacillus infection. Under this method, a leg was amputated in 2 cases for chronic osteomyelitis. In the cases treated by drainage, gas-bacillus infection developed in 1 case, and the leg was amputated. In the cases treated by the Carrel-Dakin method, it was necessary to amputate a limb in which gas-bacillus infection was present. In the cases treated by débridement and suture, 2 patients, both of whom were completely débrided, died from a gas-bacillus infection, and in 2 patients with gas-bacillus infection it was necessary to amputate a limb. When wounds are found to be infected by streptococcus, it is necessary to open the wound widely and desirable to treat the wound by the Carrel-Dakin method. Osteomyelitis is more common in those cases treated by aseptic occlusion drainage and incomplete débridement. The time which the patient must spend in the hospital is shortest under the method of débridement and suture, when successfully done.

Experiences in Rectal Surgery.—Gordon-Watson (*Brit. Med. Jour.* 1924, **1**, 559) says that the absence of sensibility to pain in the rectum has disadvantages in disease, especially since a malignant growth provided it does not pass the boundaries of the rectum by invasion may grow to considerable size without the owner's knowledge. It often happens that rectal pain is reflex in character, due to simple prostatic enlargement. It is a matter of regret that pain is generally regarded by the public as inseparable from cancer. It is common medical knowledge that cancer of the rectum is painless in its earlier stages. When treated by radical excision in this stage, the percentage of cure is probably higher than for any other part of the body, except perhaps the lower lip. Inflammatory strictures are constantly mistaken for malignant disease. A breaking down hematoma has been mistaken by the author for carcinoma. The author studied a series of 75 cases of fistula in ano, for tuberculosis, by microscopical sections and guinea-pig inoculations. Ten proved to be tuberculous, 5 of them were victims of active pulmonary tuberculosis and 5 showed evidence of tubercle elsewhere and must be regarded as cases of primary tuberculous fistulæ. Nine of these 10 cases were operated and after six months only 1 of them had healed. The author decries the bad name that colostomy suffers.

He feels that the secret of management in these cases lies in a regular daily washout, which trains the colon to act automatically, efficiently and thoroughly once in twenty-four hours.

The Treatment of Malignant Growths about the Face.—WITHERS and RANSON (*Colorado Med.*, 1924, **21**, 92) say that it has been observed that the more embryonal or undifferentiated the type of cell, the greater is its radiosusceptibility and conversely the more differentiated, highly specialized the type of cell, the greater is its radioresistance. Cells containing large amounts of chromatin in the nucleus are more easily killed than those containing little chromatin. It is common knowledge that the endothelial lining of blood and lymph vessels is very radiosensitive. Tumors having an abundance of thin walled delicate capillaries react much more quickly and favorably to radiation than corresponding tumors having a scanty blood supply. The cellular reaction to radiation depends upon the amount of radiant energy absorbed, whether it be primary or secondary. The susceptibility to short length therapy is a cellular characteristic, depending upon a definite histological structure. The normal tissue reaction to radiation and neoplastic invasion depends to a large degree upon the well-being of the body as a whole. There is sufficient data to predicate on *a priori* grounds those tissues or tumors which will prove radioresistant or radiosusceptible. The use of the radium or roentgen-ray in a given condition should require an equal amount of surgical judgment, a more complete knowledge of the pathology and a broader biophysical training than the corresponding surgical oblation demands.

Spondylolisthesis a Common Lumbo-sacral Lesion.—BOWMAN (*Am. Jour. Roent. and Rad. Therap.*, 1924, **11**, 223) says that spondylolisthesis is not an uncommon condition. It is a common cause of pain in the lower back, as shown by the frequency with which it occurs in lower back injuries. It is usually the result of trauma, the injury often being considered of minor importance. The symptoms are often not so severe as you would expect this type of lesion but are prone to get progressively worse after injury. Many of the cases now diagnosed as sacroiliac dislocations by the attending physician or surgeon that cannot be demonstrated roentgenologically are in reality, cases of spondylolisthesis. Clear detailed lateral roentgenograms of the lumbosacral region are absolutely essential in diagnosing these cases.

Acute Appendicitis in Childhood.—BEEKMAN (*Ann. Surg.*, 1924, **79**, 538) says that the earlier the diagnosis is made and operation performed, the lower is the mortality, the fewer the complications and the shorter the convalescence. The condition in children is more frequent as adolescence is approached. With the exception of children under five years of age, in whom it is extremely high, the mortality is about the same as is found among young adults. The disease is found twice as commonly in boys as in girls, while the mortality is twice as great among girls as in boys. Perforation of the appendix with spreading peritonitis or abscess formation occurs more often in children than in adults. Immediate postoperative complications are as commonly found in children as in adults with the exception of secondary

abscesses, which are seen more often. Incisional hernia follows operation in children more often than in adults. Sloughing of muscles and aponeurosis, secondary abscesses and partial evisceration of portions of the abdominal contents appear to be the causative factor. Mistakes in diagnosis would seem to be inevitable, and it would be better to err by operating.

Fracture of the Anterior-superior Spine of the Ilium by Muscular Violence.—CARP (*Ann. Surg.*, 1924, **79**, 551) says that the fracture is infrequent, 21 cases being reported. All the patients were males, a large percentage of whom were athletic and muscular. All had pain, while a snapping was felt by 45 per cent. The fragment was felt in 90 per cent. All the patients limped, 76 per cent had immediate disability, 11 per cent walked a short distance, 1 case could walk forty-eight hours later and 1 case walked about for three weeks. The majority of the cases were right-sided. The average duration of the disability in the 9 unoperated cases was twenty days. The two operated cases showed return of function in one month. End-results were excellent in all cases.

Congenital Hypertrophic Pyloric Stenosis in Infants.—COCHRAN (*California and Western Med.*, 1924, **22**, 137) states that ether anesthesia is preferable to local. The Fredet-Rammsted operation is much simpler and more quickly performed than gastroenterostomy, and therefore the best technic to follow in all cases. In most cases the differentiation between pylorospasm and stenosis is clear and only in questionable cases should fluroscopical aid be resorted to. These little patients are too sick to be loaded up with barium, unless it is absolutely necessary. Cases under observation should not be allowed to lose too much weight before resorting to surgery for after loss of 20 per cent of body weight these cases become poor risks instead of good risks. The simpler technic and earlier operating has reduced the earlier greater mortality of gastroenterostomy series.

The Treatment of Acute Empyema.—CHANDLER (*St. Barth. Hosp. Rep.*, 1924, **57**, 49) says it appears that the resection of a rib is a satisfactory method in adults, but too severe a procedure in children. The invention of new and ingenious methods of treating empyema has a peculiar fascination, and there is a great temptation to regard the favorite modification as a great advance. Recent work in chest surgery has taught much. Positive and negative pressure chambers have been discarded. The lung can be handled freely. Though compressed for many months, it can be liberated and restored to perfect function by the stripping of the thick pleura that has held it prisoner. By operating neither too late nor too soon, by freeing the lung that is bound down, by leaving no large irritant in the pleural cavity such as an unnecessarily long drainage tube, there is every reason to look for success in the great majority of cases. If the empyema has been left for a long time and the lung is bound down, immediate decortication is a more rational procedure than suction drainage, and an extended trial will probably prove it the more successful method. The figures relating to all the methods employed in the treatment of empyemata occurring in the first year of life make the prospects at this age seem very hopeless.

THERAPEUTICS

UNDER THE CHARGE OF
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The Treatment of Asthma with Combined Peptone and Vaccine.— VEITCH (*Brit. Med. Jour.*, January, 1924, p. 13) found that some cases of asthma did not react to either peptone or vaccines when given alone, so devised a system of giving the peptone and vaccine combined. His results in 24 cases treated in this manner were unsatisfactory, and no other medicinal or dietary treatment was used. The solution used was in three strengths: A. 5 cc of a 5 per cent solution equal to 0.25 gm. of peptone plus 235,000,000 organisms of an anticatarrhal vaccine of mixed strains of bacteria; B. 5 cc of a 10 per cent solution equal to 0.5 gm. of peptone plus 940,000,000 organisms of an anticatarrhal vaccine of mixed strains of bacteria; C. 10 cc of a 10 per cent solution equal to 1 gm. of peptone plus 1,880,000,000 organisms of the same anticatarrhal vaccine of mixed strains of bacteria. Injections were given every seven days. For the first four weeks half a tube of A solution per week, for the second four weeks half a tube of B solution per week, and so on, increasing in strength of dosage. The older the patient the more stubborn was the case to treatment, and the younger the patient the sooner were the signs of improvement noticed.

Further Observations on the Action of Iodid in Goiter. — JAGIC and SPENGLER (*Wien. klin. Wchnschr.*, 1924, **5**, 16) conclude that good results in cases of goiter can only be obtained by close observation of the patient, and strict individualization in the dosage of sodium iodid. In general the diffuse forms are more amenable to treatment than the nodular. Weekly observation of cases was made to determine the circumference of the neck, the body weight and the appearance of cardiovascular symptoms. Three drops of a 5 per cent sodium iodid solution were given three times a day in increasing doses. In 16 cases of goiter with thyrotoxic symptoms 8 were improved, 6 remained unimproved, and 2 showed increase of symptoms. In most cases the dose could not be increased above 5 drops three times a day. Of 36 cases of goiter without thyrotoxic symptoms 12 were improved, 17 remained unimproved and 7 cases developed conditions which indicated stopping treatment. One case of this series took 10 drops three times a day, and one 15 drops three times a day. The greatest change in the size of the goiter was also obtained in this group. Only 5 cases with marked symptoms of Basedow's disease were treated. Two showed marked improvement, particularly in the size of the thyroid gland, 2 showed increased symptoms of the disease except for a diminution in the neck circumference, while the fifth showed no improvement, and was operated on.

New Uses for Suprarenin in Clinic and Practice.—The idiosyncrasy of the patient and the variation in the activity of various suprarenal extracts still restrict the more general use of extracts of the suprarenal gland in practice. MOEWES (*Deutsch. med. Wchnschr.*, 1924, **51**, 239) recommends suprarenin (Höchster Farbwerke) in 1 to 1000 solution for reliability and constant strength. Suprarenin has been used universally to raise blood-pressure and as a cardiac and vasomotor stimulant. In the last few years it has been used extensively to counteract the symptoms which sometimes arise following injections of arsphenamine. Conditions associated with or due to abnormal irritability of the vegetative nervous system, such as urticaria, erythema and local swelling are also corrected by injections of suprarenin; 0.25 to 0.5 cc, given subcutaneously or intramuscularly, is enough to obtain the desired results in most of these conditions. In the vomiting of pregnancy, and when of pure nervous origin, excellent results have been obtained by giving 20 drops three times a day by mouth—in spite of theoretical opposition to this form of administration. Injections of 0.25 to 0.5 cc are also indicated in these cases. The vomiting and headaches following lumbar puncture have also been relieved by similar injections. Nervous disturbances of the gastrointestinal tract are also influenced by injections of suprarenin and spasm is relieved, as is also done by atropin and papaverin. In cases of chronic asthenia, such as Addison's disease, continued injections should be given, and also in cases which show real or so-called pseudovagatonic manifestations. Serious conditions have never been seen with the small doses recommended by the author.

The Present Position of Blood Transfusion.—NATHER (*Wien. klin. Wchnschr.*, 1924, **37**, 203) concludes from one hundred and fifty transfusions, which he has performed in the last year and a half, that avoidance of serious reactions during or after the transfusion can be accomplished by careful grouping of the donor's and patient's bloods, using the Moss grouping and the paraffined Percy syringe for the transfusion. He emphasizes the danger to the patient if the donor's blood cells are agglutinated. Defibrinated or citrated blood transfusions, he believes, should be discarded. The object of transfusion may be: (1) Addition of blood; (2) stimulation of the bone-marrow; (3) to stop bleeding; (4) foreign protein action, or the action of an immune substance. Results with acute hemorrhage are excellent and immediate secondary anemias are benefited not only by addition of blood to the circulation, but by stimulation of the bone-marrow, and he emphasizes the social importance of this fact for the wage-earner. In pernicious anemia it is an important preliminary to removal of the spleen. More than one transfusion is often indicated. He mentions the importance of transfusion as a hemostyptic in cases of persistent bleeding, particularly from the gums or from an ulcer of the stomach. Chronic septic processes are improved, and often can be cleared up by transfusion. A new indication first advocated by Professor Clairmont is the treatment of gastric ulcer, and the author mentions a case of inoperable ulcer of the cardiac end of the stomach in which a protracted bleeding was stopped, and pain ceased so that the patient could return to work. Cases of carcinoma which he has seen improved by transfusion he attributes to the improvement of the sepsis and the action of the blood as an immune body.

Pluriglandular Obesity and Its Treatment.—Obesity, due to pluriglandular dysfunction, may occur before or after puberty, but is usually seen in women following childbirth, immediately before or after the climacteric, or after some psychic disturbance. In all cases there is marked swelling of the fatty tissues, with a predilection for the shoulders, lumbar region, thighs and upper arm. ALEXANDER (*Deutsch. med. Wchnschr.*, 1924, **51**, 300) considers treatment of this condition with extracts of single organs, such as the thyroid or ovary, illogical and unsatisfactory, and for a long time has used lipolysin (Dr. George Herring, Berlin) with good results. Lipolysin is a mixture of the extracts of the thyroid, hypophyseal, pancreatic and genital glands; lipolysin masculin, containing an extract of the testicle, and lipolysin feminin, an extract of the ovary. Lipolysin causes at first a marked diuresis and relief of the spastic constipation, which commonly is found in these cases. During the early part of the treatment the fluid intake should be diminished, and carbohydrates and fat restricted. The best diet is one containing an abundance of vegetables and meat. The most satisfactory results with the use of lipolysin were obtained when injections of the mixture were given every other day and two tablets by mouth on the intervening day. When twelve injections have been given the tablets are administered by mouth only unless there is an increase in weight or swelling of the tissues. A total of twenty-four to thirty injections and from one hundred and twenty to one hundred and fifty tablets may be given without danger. At the termination of the regular treatment two to three injections may be given before the menstrual periods to relieve the dysmenorrhea and prevent a recurrence of the pluriglandular insufficiency which may result from the menstrual disturbance.

PEDIATRICS

UNDER THE CHARGE OF

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The Relation of Heredity to Diseases of Infancy and Childhood.—HERRMAN (*Arch. Pediat.*, 1924, **41**, 301) says that physicians have not given the subject of heredity the attention that it deserves. The remarkable progress in bacteriology is largely responsible for this neglect of the difference of the reaction of different individuals to the same external agents. It is important to detect unfavorable peculiarities and tendencies early in childhood in order that their further development may be prevented. The inheritance of physical and mental peculiarities apparently follow the same laws. Both are present in the same individual. For proper study of the laws of inheritance complete family histories and pedigree charts are essential. Tendencies and peculiarities, although on a hereditary basis and congenital, may not manifest themselves at birth, but may develop later when the indi-

vidual is called upon to bear an increased burden as a result of such causes as improper feeding, an unfavorable environment, infection or psychical shock. Inherited tendencies may manifest themselves in the appearance of one or more of a group of related conditions—in the the vulnerability of a certain organ or system, or in the appearance of congenital deformities. Good health and nutrition do not necessarily go hand in hand with resistance to the infectious diseases. The ability to develop active immunity appears to be distinct for each infectious disease, and it is probably on a hereditary basis. The ability to develop antitoxin in diphtheria acts as a dominant character. The germ plasm, although a part, is distinct from and, to a great extent, independent of the organism itself. The normal intact placenta acts as an effective barrier against the transmission of injurious substances to the fetus through the placental circulation. In time there is the best opportunity to study the relative importance of heredity and environment in the development of the human being. Acquired characteristics are not inherited. The environment cannot originate or create new qualities. The potentiality must be present. The environment may modify, hasten, retard or inhibit the development of latent qualities. Prenatal care of the mother, although of great value, has a definite limitation so far as the development of the fetus is concerned. Syphilis in the mother can be treated, disturbances of renal function can be detected, pelvic deformities can be noted, but certain fundamental defects, which have their origin in the germ plasma, cannot be influenced. At present only the worst kind of mating can be prevented by law. The best can be encouraged. A spread of the knowledge of the importance of the subject through educational propaganda is essential.

A Morphological and Quantitative Study of the Blood Corpuscles in the Newborn Period.—LIPPMAN (*Am. Jour. Dis. Child.*, 1924, **27**, 473) found that the morphology of the blood of the newborn differs in many ways from that of the adult. His study was undertaken to fill a gap in the knowledge of newborn blood during the first forty-eight hours after birth. So many changes occur at this time that a careful analysis of the variations is essential. The forty-eight-hour period has been divided into eight parts, 30 cases being considered in each interval. Counts were made of the red blood cells, leukocytes and platelets. Differential studies included the examination of 500 cells in each smear. White counts and differential studies were again made at five days to secure a further check on the material. The red blood cells at birth average 5,200,000 per c.mm. During the first six hours the count rises to 5,600,000. Following this there is a drop to 5,400,000 at eighteen hours, after which the count remains at a fairly constant level until forty-eight hours after birth. The platelets at birth average in the counts 5,200,000 per c.mm. It drops to 170,000 during the first six hours. The decrease continues until eighteen hours after birth, and is followed by a slight increase. No changes from normal were observed in the platelet counts in icterus neonatorum. The total leukocyte count at birth average 16,600 per c.mm. At twelve hours it is 22,500, after which it gradually drops to 11,300 at forty-eight hours. At five days it has decreased to 9500. The differential counts

show wide variations. The averages present curves which are often quite different from those reported in the literature. One of the striking features observed was the marked changes which may take place within a very few hours. In one instance the white cell count jumped from 25,000 to 34,000, while the polymorphonuclear cells increased from 38 to 61 per cent within six hours. It is important in any differential blood study to determine the absolute cell counts as well as the percentages. The curves often differ from each other to a great extent. The polymorphonuclear neutrophils follow closely the total white cell count, and are primarily responsible for the leukocyte curve in the newborn period. The neutrophilic melamyelocytes are very numerous in the newborn blood. Values as high as 43 per cent have been observed. Neutrophilic myelocytes are infrequent in newborn blood, but are most numerous during the first eighteen hours.

The Effect of Freezing on Diphtheria Toxin-antitoxin Mixtures.—ANDERSON and LEONARD (*Jour. Am. Med. Assn.*, 1924, **82**, 1679) examined 15 lots of toxin-antitoxin mixtures containing three L+ doses of toxin, prepared with a highly refined globulin in which 0.3 per cent tricresol was used as a preservative. This showed no increase in toxicity after freezing. Eight lots of diphtheria toxin-antitoxin mixture, prepared with a highly refined globulin, containing one-tenth L+ dose of toxin, with 0.3 per cent tricresol used as preservative, developed no increase in toxicity after freezing. Mixtures of diphtheria toxin-antitoxin prepared as stated became on the average less toxic after freezing. Mixtures prepared with three L+ doses of toxin, with 0.3 per cent tricresol, and made with an antitoxin that had been concentrated without the use of heat, showed an increase in toxicity after freezing. Diphtheria toxin-antitoxin mixtures prepared with unconcentrated antitoxin, with three L+ doses of toxin, 0.3 per cent tricresol or 0.5 per cent phenol being used, increased in toxicity after freezing. Diphtheria toxin-antitoxin mixtures prepared with unconcentrated antitoxin, with three L+ doses of toxin, chlorbutanol or chloroform being used, or without preservative, showed no increase in toxicity after freezing. Diphtheria toxin, after freezing at $-5°$ C. for forty-eight hours, showed a decrease in toxicity. In the mixtures prepared with unconcentrated antitoxin, containing three L+ doses of toxin, with tricresol as a preservative, and subsequently frozen, there became dissociated approximately twenty minimal lethal doses of toxin. This free toxin was neutralized by the addition of diphtheria antitoxin or the simultaneous administration of antitoxin, so that acute death was prevented. Paralysis and local reactions sometimes developed.

Wasting Disorders of Early Infancy.—PARSONS (*Lancet*, 1924, **1**, 1793) points out that in infantile atrophy infants after thriving normally begin to lose weight for one or more causes, such as insufficient or unsuitable food, diarrhea and vomiting, infection, hygienic surroundings or prenatal influences or constitutional causes. Many of these children can, and do, absorb a larger amount of fat per 1 kg. of body weight than normal children usually do, but a high-fat dietary may cause fat indigestion, and with diarrhea, in whatever manner produced there is diminished fat absorption. Calcium absorption is

usually very good if a sufficient supply of fat and calcium is present in the food. Many of these children absorb more calcium per 1 kg. of body weight than normal children usually do, but in a poor-fat or calcium dietary the absorption is not good. There is present in many cases faulty salt metabolism, which may result in low retention values for calcium. Protein metabolism is also faulty. The absorption of protein is normal; protein indigestion is rare, and has only been seen where there has been a large protein intake over a considerable period of time. The metabolic disturbances are essentially abnormal salt metabolism and abnormal protein metabolism, resulting in poor retention values for mineral salts and nitrogen.

Acute Appendicitis in Children.—MÜLLER and RAVDIN (*Jour. Am. Med. Assn.*, 1924, **82**, 1852) review the records of 58 patients, of whom 54 recovered and 4 died, a mortality of 6.8 per cent. There has been a marked decrease of the mortality rate in children in the past decade. This is more striking than the reduction in the mortality rate in adults. The lower mortality has been brought by early diagnosis and early reference to the surgeon for operative intervention. The mortality can be further reduced only by an earlier differentiation of these cases from the conditions that simulate it, such as pneumonia, pyelitis, Pott's disease, gastroenteritis, fecal impaction and intestinal obstruction. It is interesting to note that the low mortality rate existed in spite of the following complications: Twenty-eight cases, or 48.3 per cent, had peritoneal extension at the time of operation. Twelve of these, or 42.8 per cent, had local peritonitis, and 7, or 25 per cent, had generalized peritonitis. In 30 cases the inflammation was localized at the appendix; 29, or 50 per cent of the patients, were purged before operation. In nearly every case the purgation had been repeated. The administration of purgative before an absolute diagnosis has been established, has been the cause of more harm than any other factor connected with the disease. If it is necessary to obtain an evacuation of the bowel before a diagnosis has been established adequate results can be obtained by the use of an enema. One of the most important factors in establishing the diagnosis is a complete leukocyte count. In this series it was found to be almost constantly high.

OBSTETRICS

UNDER THE CHARGE OF

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Unusual Toxemia of Pregnancy.—HEIDLER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **63**, 249) describes the case of a woman, aged twenty-two years, who had the usual diseases of childhood and was brought to the hospital in her first pregnancy. On examination she was fairly

developed; there was no edema; the fundus of the uterus was four finger breadths beneath the tip of the sternum; a child presenting by the vertex, the head at the brim of the pelvis. The heart sounds could be heard distinctly and the pelvis was of average size. She had become unconscious at midnight preceding her admission. The patient's mother stated that several months before admission after a short period of unrest the patient had suddenly become unconscious with slight convulsive movements over the whole body, cyanosis and the expulsion of foam from the mouth. These attacks had recurred until she had twenty. A midwife was called, who sent her to the hospital, where she was admitted in an unconscious condition but otherwise not in a serious state. There were very slight disturbed motions, but deep stupor. From this the patient suddenly aroused and had to be restrained by the use of morphia; when the effect of the drug wore off she was again unruly, and complained of intense hunger and asked for food. This was followed by further unconsciousness and vomiting from which she recovered. The urine showed a faint trace of albumin and a few casts; the eyes were normal. The patient felt much better in a few days and was discharged from the hospital to her home. The diagnosis was made of intercurrent eclampsia and the patient strongly urged to report regularly to the clinic for observation; this she did not do. She went through the pregnancy without further complication and gave spontaneous birth in her home to a well-developed child, apparently healthy. Her second pregnancy ended with spontaneous abortion and her third in an abortion at six months, her fourth in normal labor at the hospital and in the fifth pregnancy she came under the observation of the writer. The patient remembered very little of the complications of her previous pregnancies, but during the present pregnancy she had several attacks of unconsciousness, from which she would suddenly recover. These attacks were without premonition, some occurring at night; mostly during the day. Some occurred while the patient was upon the street, and she was brought home in this condition. When in the non-pregnant condition she had nothing whatever of this sort. As pregnancy drew toward its close the attacks were less frequent, but an accurate history concerning them could not be obtained as no physician had ever seen her in one of the attacks. When the patient came under the observation of the writer she was well nourished, the skin was dry, the thyroid not enlarged, the face slightly reddened, the patient answered questions intelligently and was animated and there was no edema. Urine obtained by catheter was negative. A small quantity of urobilin was present. The blood showed 2,731,000 red cells; leukocytes, 5200 per c.mm. A Wassermann reaction was negative. A minute examination of the blood for thrombocytes and fibrinogen revealed nothing extraordinary. The neurological and psychological examination revealed no scar on the tongue; reaction to electricity normal; no evidence of hysteria and no signs of epilepsy. The patient's labor was spontaneous, with recovery of mother and child normal. To sum up the case, a woman aged twenty-two years, without hereditary history of nervous or other disease, in five pregnancies had during the first, attacks of unconsciousness, with very slight albuminuria; this pregnancy terminated in normal labor;

the following pregnancies showed the same phenomena and they developed so soon after the pregnancy occurred that their appearance led the patient to suspect that she was pregnant before any other symptom had appeared. There was absolutely no sign of any such condition when the patient was not pregnant. An effort was made to test the patient by injecting adrenalin, as it has been found that under certain diseased conditions of pregnancy, adrenalin produces an unusual reaction; in the case described no such reaction occurred; this was repeated with negative result. Pilocarpin was next tried, with negative result; to test the function of the liver milk was used, and an examination made for leukocytes with the usual result. Comparing this case with one reported by Curschmann, the suggestion of cortical epilepsy is made as the probable cause. In Curschmann's case there were Jacksonian attacks and hemiparesis from which the patient recovered.

Cerebral Symptoms Produced by the Toxemia of Pregnancy.—APEL (*Zentralbl. f. Gynäk.*, 1923, **4**, 160) reports the case of a woman in her fourth pregnancy, aged twenty-six years, brought to the clinic alleged to have eclampsia. An accurate history could not be obtained, and her appearance suggested the somnolent condition which eclampsia often manifests between convulsions. It was stated that at twelve years of age she had measles severely, followed by paresis of the extremities, persisting for several days. She had otherwise been apparently healthy, of average intelligence and ability. When eighteen years old her first child was born, a year afterward a second without special complications, a third birth followed and 2 of the children perished—1 shortly after birth and 1 three weeks later from spondylitis. She had naturally been greatly disturbed by the loss of the children, but the present pregnancy had proceeded up to the time of admission without complications. She was taken suddenly during the night with a convulsive attack, after which she complained of headache and remained in bed for a day; she was then able to resume her housework, when two other convulsions followed and she was sent to the hospital. On examination she was well developed and vigorous, and the internal organs showed no pathological condition. The reflexes were practically normal, except the plantar reflex which was increased, while the reflex of the abdominal wall was absent. Variations in sensations could not be demonstrated. The tongue showed no injury; the pulse and temperature were normal. The systolic blood-pressure was 120 mm., mercury; the urine was normal. The size of the uterus indicated seven months' pregnancy. Heart sounds were heard. The cervix uteri admitted one finger and the cervix was not obliterated, but the membranes could be felt and showed no signs of pressure. During the examination the patient had an attack: The head was slowly turned to the left; both arms were extended then flexed and turned toward the left; the right arm and leg were then extended and clonic convulsion occurred. During the attack the muscle tone was relatively diminished; the mouth was widely open; the tongue was not bitten; both eyeballs turned sharply toward the left; the pupils reacted directly after the convulsion and at the end of the attack, which lasted half a minute, there was very little cyanosis and secretion of saliva.

The patient did not become comatose, and speedily became conscious. The attack was not typical of eclampsia and 0.4 gm. of luminal was given by intramuscular injection. These attacks returned and were uninfluenced by sedatives and narcotics. The urine remained normal; the vascular system showed no variation; the temperature rose to 99 to 100° F., and the same night a living male child was suddenly born, and the placenta expelled with very slight loss of blood. After the expulsion of the child the patient's condition remained practically the same; the attacks recurred and were not controlled by luminal and morphin. The condition of the nervous system was essentially the same and there was a slight facial paresis on the left side. An examination of the eyes showed a slight projection in the optic nerve on the right side. Convulsions then became very frequent, the left side of the body showing much more violent convulsions than the right. The pulse rose to 100; the temperature fell somewhat; the patient became comatose and was controlled somewhat by scopolamin. Abundant tracheal rales were present, the sputum was retained and the patient seemed in a very critical condition. The number of attacks had reached more than 100. On the following day after a succession of attacks in the early morning the patient was transferred to the neurological clinic, and after a brief period the attacks ceased and the patient was discharged. The writer is positive that this was not eclampsia of the usual form; that it was toxemia of pregnancy there can be no doubt and that it was accompanied by some cerebral lesion of a chronic and latent nature he considers also to be a most rational explanation. He quotes numerous authors who report anomalous cases of convulsions in parturient women, and among them the case of a woman who when two years old had been seriously ill with measles and thirteen years later developed epilepsy from cranial and cerebral irritation. Examination of the cranium by the roentgen-ray showed a deposit of calcareous matter in the cranial wall and the resulting condition of chronic irritation.

GYNECOLOGY

UNDER THE CHARGE OF

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Tests for Cure of Gonorrhea in Women.—In undertaking the treatment of gonorrhea in the female, it is important to know when it is safe to discharge the patient as cured, which is often a difficult thing to determine. According to ABRAHAM (*Lancet*, 1924, **206**, 429), the

first criterion is that all clinical signs of the disease must have disappeared. By this is meant: (1) That there is no induration of Bartholin's glands, or sign of inflammation around their orifices; (2) that the urethra appears normal on inspection externally, palpation through the vagina, and urethroscopical examination; (3) that the paraurethral crypts, especially Skene's tubules, show no inflammatory signs; (4) that the vaginal introitus is normal in color, with no inflamed tags or crypts around it, and that pain is not complained of when a speculum is passed; (5) that the cervix appears normal, the secretion clear, and no erosion is present; (6) that the uterus and tubes, on bimanual examination, are apparently free from disease; and (7) that the anal orifice seems normal, and there are no signs of inflammation or discharge in the anal canal on passing a speculum. The second essential desideratum is that all bacteriological signs of disease should be absent. Evidence on this point can only be accepted if the following technic, and the precautions mentioned below are observed in making the examination: (1) Smears taken from the urethra by means of a sterile platinum loop inserted half an inch down, should be negative for pus cells and gonococci in a patient who has had a provocative injection of 1 cc of gonococcal proteose twenty-four hours previously. The urethra should be massaged gently forward before the loop is inserted, and the surgeon should assure himself that the patient has not passed urine for some hours before the examination; (2) the urine held for some hours before examination, should be clear, acid, free from ablumin and contain no gonococci or pus, when the centrifuged deposit is examined under the microscope; (3) smears taken from the orifices of Bartholin's glands and from Skene's tubules should be negative; (4) smears taken from the cervix by means of a platinum loop should be negative for gonococci and pus, when taken before menstruation, just after menstruation has ceased and twenty-four hours after a provocative injection of 1 cc of gonococcal proteose; (5) smears taken from the anal canal should be negative for the gonococcus. The anus is a fruitful source of reinfection. Gonococci can often be found there when they are absent elsewhere in women. Nothing is said about attempting to grow the gonococcus from smears, because he believes the method is useless. In regard to the complement-fixation test, Abraham has found that in the acute stages of a urogenital infection the test is useless as a means of differentiating between a gonococcal and non-gonococcal infection, but if the infection has existed from two to six months, then a negative test indicates that the disease is non-gonococcal, in other words, the reaction is specific. If a positive test is present a year after all clinical and bacteriological symptoms have disappeared, it may be neglected for all practical purposes. In brief, in the early stages of gonorrhea, the test is not sufficiently powerful to diagnose the disease, in the middle stages it will differentiate between gonococcal and non-gonococcal disease, and in the convalescent stage it is too delicate for use as a practical sign of cure.

Roentgen Therapy of Benign Uterine Bleeding.—Basing his observations on the treatment of more than 500 cases of uterine fibroids and uterine bleeding not due to malignancy, WILLIAMS (*Am. Jour. Roentgenol.*, 1924, **11**, 252) states that the cases in which this form of

therapy is indicated are as follows: (1) Fibroid tumors of the uterus, except the pedunculated submucous type, or those showing degeneration; (2) functional menorrhagia and metrorrhagia of adolescence; (3) menorrhagia and metrorrhagia without evidence of gross pathology and most commonly observed in the fourth decade; (4) menorrhagia and metrorrhagia due to metritis or endometritis of hypertrophic or polypoid nature. A contraindication for this treatment is infection, active or latent, in the pelvis. An old quiescent infection may be converted into an active process by radiation therapy. When there is some complicating lesion requiring surgery for relief, this form of treatment should be used only as an adjuvant, for instance, to check hemorrhage. From the foregoing observations it should be realized that a complete pelvic examination should be made by a competent diagnostician before instituting this treatment. About two years ago a new technic was developed which has been constantly used since that time. Instead of using multiple portals of entrance, the treatment is given through a single large one. Where there is a large tumor present, the portal is sufficiently large to include the entire tumor. A fibroid uterus the size of a five months' pregnancy will not be palpable above the symphysis and will be but little above normal size after four treatments. Larger tumors extending to the navel or above gradually diminish in size, the full effect of the treatment not being realized in less than one year. Radiation therapy controls hemorrhage in these cases through its effects on the ovaries and on the development of the Graafian follicles. There is some diversity of opinion as to whether the reduction in size of a fibroid uterus is due to the direct action of the rays on the tumor or whether it is secondary to the effect on the ovaries, it having been known for a long time that these tumors do diminish in size after the menopause. From the author's own experience, he believes that the reduction of the tumor is due to the direct action of the rays. If after roentgen-ray therapy, the patient complains of pain in the pelvis, especially if it be a unilateral pain, or develops fever or chills, the treatment should be discontinued. These symptoms indicate the presence of some infectious process in the pelvis which has been overlooked. A single treatment will probably not seriously activate a latent infection, but repeated treatments most certainly would do so.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Medium for the Inhibition of Spreaders and the Differentiation of B. coli and B. aërogenes.—By adding 1/100000 of crystal violet to Levine's eosin methylene blue agar, SKINNER and MURRAY (*Proc. Soc.*

Exper. Biol. and Med., 1924, **21**, 188) found that none of the 50 strains of spore-forming organisms (spreaders) developed in twenty-four hours and 21 developed only slightly in forty-eight hours, the remainder never growing. The Bacillus coli colonies were black or dark bluish-violet by transmitted or reflected light, with dark centers reaching to the edge or nearly so. They tended to a decided green metallic sheen. The Bacillus aërogenes colonies were pink or light lavender by reflected light, by transmitted light, dark centers not reaching more than half way to the edge. The colonies were sticky, showing a decided tendency to run together (in contradistinction to the Bacillus coli colonies). There was no metallic sheen. In checking unknown colonies procured from soil sewage, feces and polluted stream water with the Voges-Proskauer test, it was found that 94.4 per cent of Bacillus coli agreed by the two methods and that 93 per cent of the Bacillus aërogenes agreed.

Studies Concerning the Significance of Streptococcus Hemolyticus in Scarlet Fever.—Since Streptococcus hemolyticus is almost constantly present in the throats of individuals suffering from scarlet fever, and since this organism is the preponderant causative agent of such septic complications of the disease as otitis media, adenitis, interstitial nephritis, arthritis and septicemia, many have regarded streptococci as the etiological agent of the disease. Moreover, since the development of a technic for the differentiation of biological types of Streptococcus hemolyticus by Dochez, Avery and Lansfield, various investigators have found that the type of hemolytic streptococcus found in the throats of scarlet-fever patients is in general a specific type readily distinguishable from the types of Streptococcus hemolyticus causing other kinds of angina and septic conditions in general. Recently DOCHEZ (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 184), assisted by SHERMAN, has been able to produce in guinea-pigs a condition resembling in its main features certain phenomena of scarlet fever by the injection of a scarlatinal type of Streptococcus hemolyticus. Being impressed by the similarity of the symptom-complex in guinea-pigs to human scarlet fever, the author immunized a horse. It has been found that the immunized horse serum will neutralize the rash locally on the skin in human cases of scarlet fever. This cutaneous blanching was more conspicuous than that obtained under similar circumstances from the use of convalescent scarlatinal serum. The authors state that "Such a sequence of observations undoubtedly again throws the balance of evidence in favor of Streptococcus hemolyticus as the causative agent of scarlet fever." They liken the disease to diphtheria, in that the principal localization of the infection is in the throat, where the organism produces a toxin which gives rise to the general symptoms and the rash. Furthermore, they suggest that the immunity in scarlet fever is probably antitoxic in character and the blanching represents the neutralization of the toxin *in situ*.

Reactions of the Urinary Bladder in Canine Anaphylaxis.—As an index to possible smooth muscle reactions, MANWARING, HOSEPIAN, ENRIGHT and PORTER (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 284) studied the pressure changes in the urinary bladder during canine

anaphylactic shock, with parallel tracings of the changes in the arterial blood-pressure. The dogs were sensitized to horse serum according to Weil's method and were tested by intravenous injections of 0.5 to 2 cc horse serum per 1 kg. of body weight about twenty-one days after the final sensitizing dose. The intracystic pressure was recorded by means of a glass catheter, and the abdomen was opened to avoid error from changes in intra-abdominal pressure. In typical anaphylactic shock the arterial pressure fell precipitously to about 35 mm. Hg. by the end of forty-five seconds, gradually decreasing to about 25 mm. Hg. by the end of ninety seconds. Recovery usually began about the twelfth minute, the blood-pressure being restored to normal in from sixty to ninety minutes. During the first forty-five to seventy-five seconds the intracystic pressure showed no recordable change, after which time it gradually increased, usually reaching a maximum of from 25 to 50 mm. Hg. by the end of two and a half minutes and returned to normal by the seventh minute. "Assuming that the cystic reactions thus recorded are reliable, indices to smooth muscle reactions in other parts of the body," the authors concluded "That in typical canine anaphylactic shock the smooth muscle structures are not thrown into contraction until the shock is fully established, as determined by the fall in arterial blood-pressure. The smooth muscle reactions, therefore, apparently played no role in the initiation of the shock. They also apparently have little or no effect on the duration or severity of the shock as determined by the changes in arterial blood-pressure." In an instance of rapidly fatal canine anaphylaxis the observations were such as to suggest that smooth muscle reactions became the dominant factor during the later stages of the shock and were apparently the immediate cause of death. Even in this type of shock, however, the smooth muscle reactions apparently played no part in initiating the shock.

Attempts to Separate the Active Constituent of Ragweed Pollen.—As ragweed appears to be the chief cause of hay-fever in this country, BAUMAN, CHUDNOFF and MACKENZIE (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 226) deemed it advisable to attempt to separate the substance in the pollen which is responsible for the sensitization of hay-fever patients. It was found that the active substance could be completely extracted from ragweed pollen with 3 per cent ammonia and that it could be quantitatively removed from the ammonia extract by precipitation with acetone. As prolonged dialysis of the ammonia extract against 5 per cent sodium chloride failed to remove the active substance, it was inferred that it was in the form of a large molecule or aggregate. The "globulin fraction" seemed to be the more active, even when dialyzed for a number of days in collodion sacs, and the authors hope that more data may be obtained by a study of the behavior of this fraction.

Recovery of Bacillus Histolyticus from Human Feces.—Having recently recovered a strain of Bacillus histolyticus from a sample of arable soil in California, HALL (*Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 198) has been able to isolate another strain of the same organism from the stool of a healthy prisoner in San Quentin Prison. The spore formers were recovered after heating to 80° C. for twenty minutes, using

deep brain medium for the initial culture and deep agar for isolation of the anaërobes. The strain was morphologically and culturally typical and, though not refusing to grow on the surface of solid media, preferred anaërobic conditions. The microörganism was exceedingly virulent when injected into a guinea-pig's leg. The author states that the finding of Bacillus histolyticus in human feces, as well as in cultivated soil, establishes a certain amount of evidence to explain its occurrence in wounds where conditions are favorable for contamination with fecally polluted soil.

HYGIENE AND PUBLIC HEALTH

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An Immunizing Strain of the Virus of Poliomyelitis.—Flexner and Amoss (*Jour. Exper. Med.*, 1924, **34**, 625) present certain facts regarding the virus of poliomyelitis. They show that strains of the virus exist in nature, which under some circumstances induce paralytic and lesser effects in monkeys, the inclination of which is toward amelioration terminating in recovery, instead of, as had been observed in the past, intensification leading to death. This latter consideration may in time come to have practical significance. The qualities which distinguish the attenuated strain of the virus raise the question whether the mild grade of activity is an inherent property, or whether it is a product of the mild putrefactive changes taking place in the human tissues. No answer can be returned at present to this question, which, however, may not prove entirely beyond experimental determination. It has been ascertained by experimental tests that the modified form of poliomyelitis through which the inoculated monkeys pass, and from which they recover, leaves them protected against the action of a highly virulent strain of the virus of poliomyelitis. The mild or attenuated strain of the virus seems to be of a fixed degree of potency, having neither increased nor decreased perceptibly in the two years during which it has been under study. Unless the virus was modified by the putrefactive process occurring in the original human brain and cord, it is obvious that wide disparity exists between the effects induced by the strain in the human being from whom it was derived and the monkeys into which it was inoculated. The former shows very severe acute lesions in the spinal cord and medulla, to which the death is attributable; the latter shows relatively mild lesions from which recovery, either complete or nearly complete, tends to take place.

Investigations on the Control of Hookworm Disease. XXXII. Methods of Measuring Human Infestation.—CORT (*Am. Jour. Hyg.*, 1924, **4**, 213) recommends certain modifications of administrative procedure in hookworm control work, which seem to be of far-reaching significance: (1) The use of the egg-counting technic in the examinations of preliminary surveys will give quantitative data that will make it possible to adequately plan control measures, and in certain areas will undoubtedly alter the viewpoint of the administrator in regard to the need of control work; (2) the use of the egg count, in evaluating treatment, will make possible the saving of the expense of routine reëxaminations; (3) finally, as a yardstick to measure the results of the control measures, the use of the egg count will place the hookworm campaign on an entirely new scientific basis and make much easier its justification to legislative bodies and the public in general.

The Cause of Influenza.—The findings of Olitsky and Gates, with reference to Bacterium pneumosintes as the causative agent in influenza, have been more or less confirmed by Gordon, in England, and Lister, in South Africa. On the other hand, several investigators have obtained negative results, some of which have not been published. DETWEILER and HODGE (*Jour. Exper. Med.*, 1924, **39**, 43) have studied the question in the epidemic experienced in Toronto during the past winter. They investigated 6 cases of epidemic influenza in various stages of the disease. They found suspicious cultures of bodies resembling Bacterium pneumosintes in 3 cases—twice from the lung filtrates of inoculated animals and once from the filtrate of nasopharyngeal washings direct. In these instances material was obtained within thirty-six hours of the acute onset, thus confirming the observations of Olitsky and Gates. Macroscopical and microscopical findings in the lungs of inoculated animals were uniformly negative.

Viscosity and Toxicity of Arsphenamin Solutions.—VOEGTLIN, JOHNSON and DYER (*U. S. Pub. Health Rpts.*, 1924, **37**, 179) studied the relation of certain physico-chemical properties of solution of arsphenamin to the toxicity of the drug. It was shown that there is a relation between toxicity and viscosity, the higher the latter, the higher will the former be found. The handling of the drug determines largely the degree of viscosity; thus, on allowing solutions to stand for a short time there is a readjustment with a reduction of viscosity, and, in consequence, of toxicity. The studies have a bearing on the immediate so-called "nitritoid" reactions that may follow the administration of arsphenamin.

A Study of the Treatment and Prevention of Pellagra.—GOLDBERGER and TANNER (*U. S. Pub. Health. Rpts.*, 1924, **39**, 87) emphasize again the importance of fresh meat and milk in the treatment of pellagra. Their summary is as follows: (1) Eight well-marked, though not very severe (mainly dermal), cases of pellagra were treated with fresh beef as the only known therapeutic element in the diet. (2) In all 8 cases clinical improvement following the inauguration of the beef treatment.

(3) In 4 of these cases the treatment with beef followed an unsuccessful period of treatment with gelatin, the contrast in results tending to emphasize, on the one hand, the inadequacy of gelatin, and, on the other, the therapeutic potency of fresh beef. (4) The preventive value of milk was tested by daily supplementing the basic diet of a group of 29 inmates of the Georgia State Sanitarium with approximately 40 fluidounces (1200 gm.) of buttermilk. (5) None of these patients developed any evidence of pellagra at any time during the period of observation, which, for 25 of the group, lasted one year, although it is believed that without the buttermilk or equivalent supplement upward of 40 or 50 per cent of the group would have developed pellagra within a period of three to eight months. (6) Fresh meat and milk contain the essential pellagra-preventive factor or factors. (7) It is estimated that about 4 to 4½ ounces (125 gm.) of fresh beef (lean round steak) and not over about 40 fluidounces (1200 gm.) of buttermilk will suffice to prevent pellagra in all but very exceptional instances. (8) Fresh butter (from cows largely pasture-fed) ingested daily in quantities averaging approximately 125 to 135 gm. (butter fat, 100 to 110 gm.) failed to prevent pellagra in several instances in which it was tried. (9) Cod-liver oil ingested daily in quantities averaging upward of 2 gm. per kilo of body weight failed to prevent pellagra in several instances in which it was tried. (10) The primary etiological dietary factor in pellagra is a faulty protein (amino-acid) mixture, a deficiency in some as yet unrecognized dietary complex (possibly a vitamin), or some combination of these.

Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum.—Hooker (*Jour. Immunol.*, 1924, **9**, 7) states that following toxin-antitoxin injections a noteworthy proportion of human subjects became hypersensitive to horse serum, as shown by specific endermal reactions. He discusses the pertinence of this observation to serum therapy in general, and recommends that, in order to avert the widespread and disadvantageous influence which such induced hypersensitiveness is likely to exert upon the use of therapeutic horse sera, some other animal be chosen for the production of that antitoxin which is destined for use in toxin-antitoxin mixtures.

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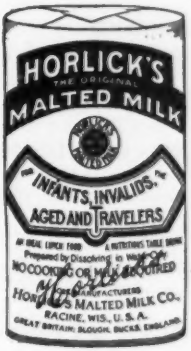

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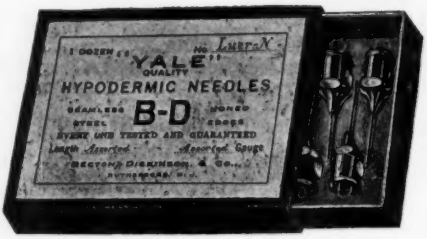

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